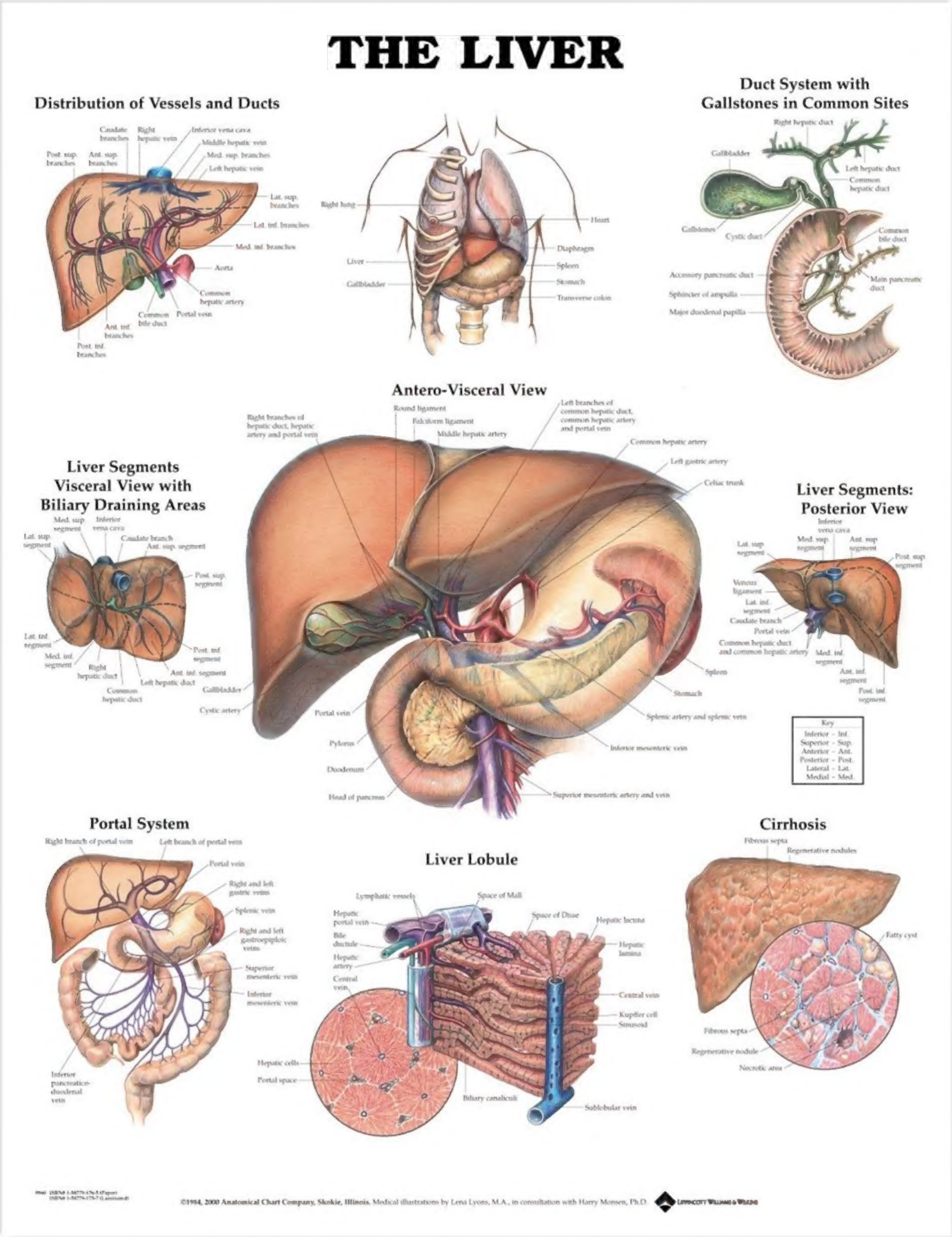

THE LIVER

Distribution of Vessels and Ducts

Duct System with Gallstones in Common Sites

Antero-Visceral View

Liver Segments Visceral View with Biliary Draining Areas

Liver Segments: Posterior View

Portal System

Right branch of portal vein
Left branch of portal vein
Portal vein
Right and left gastric veins
Splenic vein
Right and left gastroepiploic veins
Superior mesenteric vein
Inferior mesenteric vein
Inferior pancreatico-duodenal vein

Liver Lobule

Cirrhosis

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Imbaba fever hospital

ASCITES & SBP

Overview of ascites

Definition

1- Ascites is defined as **pathologic accumulation of fluid** within the peritoneal cavity.

Natural history

1- Ascites is the most common clinical manifestation of **hepatic decompensation**

2- ≈ **50%** of patients with cirrhosis will develop ascites within 10 years

3- Once ascites occurs, the 2 – year survival rate is **50%**

4- Ascites becomes unresponsive to diuretic therapy in **10%** of patents with cirrhosis

5- Once ascites becomes refractory, the 1 – year survival rate is **25%**

Pathogenesis in the setting of cirrhosis

1- **Portal hypertension:** → excess formation of fluid within the congested hepatic sinusoids; the fluid overwhelms intrahepatic lymphatics and weeps across the liver

2- **The overflow theory:** a stimulus arising from the liver results in a primary increase in plasma volume through increased renal sodium retention

3- **The underfill theory:** when ascites formation begins, the intravascular fluid compartment contracts, with an increase in the plasma oncotic pressure and a decrease in portal venous pressure; this results in 2ry increase in renal sodium retention as compensation

4- **The peripheral arterial VD theory:** → increase in vascular capacity and decrease in effective plasma volume, which results in 2ry increase in renal sodium retention

Evaluation of the patient with ascites

1- History:

- Often reveals clues to alcoholic liver disease or chronic viral hepatitis
- Acute onset of uncontrollable ascites can be associated with BCS
- Ascites associated with fever and/or abdominal pain may indicate ascetic fluid infection or malignancy
- Exclude other causes of ascites other than liver disease
- The most common symptom of ascites is an increase in abdominal girth accompanied by weight gain, frequently with LL edema

2- **Physical examination:**

- Findings suggestive of cirrhosis and portal HTN: e.g.
    - Spider telangiectases
    - Asterixis
    - Splenomegaly
    - Palmar erythema
    - Abdominal wall collateral vessels
- Findings in ascites
    - Full bulging abdomen
    - Shifting dullness evident when peritoneal fluid > 1500ml
    - Abdominal wall hernias common with ascites
- Evaluation of the underlying liver disease:
    - Detection of the cause of cirrhosis is an essential part of the evaluation for ascites that my result in effective treatment
    - The underlying liver disease should be staged by Child-Turcotte-Pugh and MELD scores

3- **Abdominal US:**

- Detect amount of 100ml of ascetic fluid
- Confirm the presence of portal HTN: e.g. spleen > 12 cm maximum dimension and enlarged portal vein
- Detect ovarian or mesenteric masses & differentiate obesity from ascites

4- **Grades of ascites:**

- Grade 1: detectable only by careful physical examination

- Grade 2: easily detected but relatively small amount
- Grade 3: obvious but not tense
- Grade 4: tense

5- Differential diagnosis

Cause	Clinical clues
Cardiac ascites	Setting and examination findings suggestive of heart failure
Malignant ascites	Setting of known malignancy and absence of stigmata of liver disease; often abdominal pain and profound weight loss
TB ascites	Persistent abdominal pain and fever; often extraperitoneal tuberculosis
Nephrotic ascites	Anasarca and substantial proteinuria in a diabetic patient
Pancreatic ascites	Follows episode of severe acute pancreatitis or occurs in the setting of chronic pancreatitis

Tapping of ascites

Indications

1- **New onset** ascites for DD (see below)

2- **Routine** on hospital admission or readmission of patients with ascites

3- Symptoms or signs suggestive of **ascetic fluid infection** (i.e. fever, abd. Pain , increased WBCs, encephalopathy or renal impairment) (see below)

4- Temporarily in patients with **refractory ascites** and/or causing respiratory distress ± LL edema (see below)

Complications

1- **Fluid leak** at the site if a Z tract is not used

2- Abdominal wall **hematoma**

3- Inadvertent bowel **perforation**

4- Hypovolemia: as the ascites reaccumulates at the expense of the circulating volume (esp. LVP if albumin not used)

5- Encephalopathy: due to electrolyte disturbance (®)

6- Hepatorenal syndrome (®)

Ascitic fluid tests

1- **Ascitic fluid cell count is the most important test:**
  - ≥ 250 PMNs → infection
  - Any inflammatory cause of ascites can lead to neutrocytic ascites
  - In bloody ascites (RBCs > 10,000/mm^3) 1 PMNs is subtracted from the cell count for every 250 RBCs to correct for PMNs that enter the fluid with the blood

2- **Culture results are optimized by:**
  - Immediate inoculation of aerobic and anaerobic blood culture bottles with 10 ml of ascetic fluid at the bedside (sensitivity ≈ 90%)

3- **Ascitic fluid albumin:**
  - Necessary to calculate SAAG
  - SAAG of ≥ 1.1 g/dl is 97% accurate in detecting portal HTN

4- **Ascitic fluid total protein:**
  - Help in detecting the cause of ascites
  - Values < 1 g/dl indicate high risk of ascetic fluid infection

Precautions

1- **Fresh frozen plasma or platelets:**
  - Routine prophylactic use not recommended because bleeding is very uncommon
  - The only contraindication to paracentesis are DIC or primary hyperfibrinolysis

2- About 6 -8 of 25% **albumin infusion** / L of fluid removed:
  - For paracentesis ≥ 5 L of fluid to prevent reaccumulaion & electrolyte disturbances & circulatory dysfunction.

Large volume paracentesis (LVP)

1- Defined as removal of ≥ 5 L of fluid.
2- Associated with more rapid resolution of tense ascites than diuretic therapy
3- Not more than every 2 weeks even in patients with no urinary Na excretion
4- I.V volume expanders not necessary for paracentesis < 5 L of fluid

5- If ≥ 5 L removed give albumin infusion
6- Used at least temporarily in refractory ascites

Technique

1- Passing a steel 22-gauge needle by a Z – tract technique below the level of percussed dullness either in the left lower quadrant (2 fingers breadths cephalic & 2 finger breadths medial to the anterior superior iliac spine) or in the midline between the symphysis pubis and umbilicus

Criteria for safe therapeutic paracentesis:

1- Tense ascites
2- LL edema
3- Child's grade B
4- Urinary Na > 10 mmol/24 h
5- Serum bilirubin < 10 gm/dl
6- Serum creatinine < 3 mg/dl
7- Prothrombin > 40%
8- Platelet > 40,000 /mm^3

Ascitic fluid tests

Routine	Optional	Unusual	Unhelpful
Cell count	Gram stain	TB smear/culture	PH and lactate
Culture	Glucose	Cytology	Cholesterol
Albumin	LDH	Triglyceride	Alpha fetoprotein
Total protein	Amylase	Bilirubin	Fibronectin

Ascitic fluid clues regarding the cause of ascites:

Causes of ascites	Ascitic fluid clues
Cirrhotic ascites	SAAG ≥ 1.1 g/dl- AFTP < 2.5 g/dl (usually)
Cardiac ascites	SAAG ≥ 1.1 g/dl- AFTP ≥ 2.5 g/dl
Peritoneal carcinomatosis	SAAG < 1.1 g/dl- AFTP ≥ 2.5 g/dl- usually malignant cells by cytology
T.B ascites	SAAG < 1.1 g/dl(without cirrhosis)- AFTP > 2.5 g/dl(without cirrhosis)- WBCs > 500/mm^3(lymphocytes predominance)
Chylous ascites	SAAG < 1.1 g/dl- AFTP ≥ 2.5 g/dl- Triglycerides in ascites >serum (usually > 200mg/dl) – milky

Nephrotic syndrome	SAAG < 1.1 g/dl- AFTP < 2.5 g/dl
Pancreatic ascites	SAAG < 1.1 g/dl- AFTP ≥ 2.5 g/dl – Amylase in ascites > amylase in serum (often > 1000u/l)

Classification of ascetic fluid infections:

Category	Ascitic fluid analysis
Spontaneous bacterial peritonitis	PMNs ≥ 250/ mm^3, single organism
Culture- negative neutrocytic ascites	PMNs ≥ 250/ mm^3, negative culture
Monomicrobial non-neutrocytic bacterascites	PMNs < 250/ mm^3 , single organism
Polymicrobial bacterascites	PMNs < 250/ $mm^{3,}$ multiple organisms
Secondary bacterial peritonitis	PMNs ≥ 250/ mm^3, multiple organisms

Treatment and follow up of hepatic ascites

1- **Rest in bed:** this improves renal blood flow and leads to diuresis

2- Identifications of possible precipitating factors:

- Dietary indiscretion
- GIT bleeding with volume and blood resuscitation
- HCC with or without portal vein thrombosis
- NSAIDs
- Iatrogenic (i.e. saline administration)
- Noncompliance with diuretics

3- Sodium restriction is the mainstay of treatment:

- Sodium balance occurs when sodium intake = sodium loss
- Na intake = dietary intake + all medically related Na administration
- Na loss = insensible (≈ 5 mmol/day) + fecal (≈ 5 mmol/day) + urinary sodium excretion
- The goal is: Na intake of 2 gm/day (88mmol/day)
- A low salt diet alone eliminates ascites in only 10% of patients
- In severe cases: Na restriction to 22 mmol/day (0.5 gm/day) is necessary

4- Water restriction:

- To 0.5 – 1 L/day necessary only if the plasma Na < 125mmol/L

5- Stepwise diuretic approach:

- **The main therapy:** for cirrhotic ascites is Na restriction + diuretics (≈ 90 % respond to this therapy)
- **Indications**:
    - Moderate to tense ascites
    - Positive sodium balance while on a Na restricted diet
- **The most effective regimen:**
    - Combination of 2 diuretics acting on different sites of the nephron (spironolactone + furosemide) which leads to short hospitalization + normokalemia
    - Starting doses → spironolactone 100mg + furosemide 40mg once daily. This ratio of K sparing / wasting diuretics → fewer k abnormality
    - Doses of both drugs should be increased while maintaining the same ratio (e.g. sp. 200mg + lasix 80 mg)
    - Maximum doses → spironolactone 400mg + lasix 160mg once daily
- **Spironolactone:**
    - K- sparing diuretics that act at the aldosterone sensitive Na channels in the distal nephron & collecting ducts (Aldosterone antagonist)
    - The drug of choice for single agent therapy of ascites
    - Less potent natriuretic than furosemide so, hypokalemia is less likely
    - Prolonged half life (up to 5 – 7 days) so, allowing once daily dosing
    - If gynecomastia occur → Amiloride 10 – 15 mg / day
- **Furosemide:**

- Loop diuretic
- Side effects: hypokalemia, hyponatremia and volume depletion

6- Complications limiting diuretic use:

- Azotemia (the most common limiting factor)
- Electrolyte abnormalities: severe hypokalemia & severe hyponatremia (< 128mmol/L)
- Intravascular hypovolemia
- Hepatic encephalopathy

7- Factors used to assess treatment response and complications:

Physical examination	24 – hr urine	Blood chemistry
Weight Ascitic fluid volume Peripheral edema Encephalopathy	Volume Na excretion	Na K Creatinine

- **Collection:**
  - A 24 hr urine collection should be obtained for quantitation of Na, K and creatinine
  - Completeness of collection is assessed by creatinine excretion of > 10mg / kg/day in females and > 15mg/kg/day in males
  - If specimen is incomplete, a urinary ratio of Na to K > 1 usually correlates with a 24 hr sodium excretion > 78 mmol.
- **The goal is:**
  - Negative Na balance + weight loss of 0.5 kg/day (if LL edema the patient can tolerate greater rates of Na excretion & more rapid weight loss 1 kg/day)
- **Diuretics should be ↑ after 3 days:**
  - If no ↑ in urinary Na excretion or ↓ in body weight

- **The goal of Na excretion:**
  - > 78 mmol/day (88mmol/day when ≈ 10 mmol/day of non urinary losses is added to 78 mmol/day of urinary losses)
- **If treatment failed** despite urinary Na excretion > 78 mmol/day: → dietary non compliance

8- Refractory ascites

- **Definition:**
  - Ascites that cannot be mobilized or early recurrence of ascites (i.e. after therapeutic paracentesis) that cannot be satisfactorily prevented by medical therapy [loss of weight < 200 gm/day to salt, fluid restriction and spironolactone 400mg + lasix 160 mg for at least 2 weeks]
- **Types:**
  - Diuretic resistant: lack of response to dietary sodium restriction and intensive diuretic treatment
  - Diuretic intractable: development of diuretic induced complications that preclude the use of effective diuretic doses
- **Causes:**
  - Salt retention: treated by tight regimen
  - Low salt syndrome: stop diuretics + fluid restriction for few days then resume diuretic therapy
  - TB peritonitis (immunocompromized patient)
  - Malignancy e.g. HCC
  - Marked hypoalbuminemia: treated by albumin infusion with adequate dose
  - Impaired kidney functions
  - Weak or low dose diuretics
- **Treatment:**
  - LVP (large volume paracentesis) ®
  - TIPS (transjugular intrahepatic portosystemic shunt)

© In patients who require frequent LVP and have a favorable post TIPS outcome by MELD score

© Significantly and promptly ↓ the portocaval pressure gradient

© Effective in about 90%

© Improvement is noted within 1-3 months

© Most patients need continued diuretic therapy after TIPS

© Compared with LVP, TIPS associated with: better long term control of refractory ascites, improved transplant free survival & High frequency of hepatic encephalopathy (40%)

- PVS (peritoneovenous shunting) → Now rarely used (Le veen shunt) because of poor long term patency, excessive complications and no survival advantage.
- Liver transplantation → the only life saving therapy for patients with refractory ascites whose 1- year survival rate is 25% without this treatment. If no hepatorenal syndrome → better outcome

Spontaneous bacterial peritonitis

Incidence

1- Occurs in about 10% of cirrhotic patients with ascites

2- SBP is the most common type of ascitic fluid infection

3- For every one-point increase in MELD score, the risk of SBP increased by 11% (in one study)

4- Proton pump inhibitors associated with an increased risk of SBP

Pathogenesis

1- Causative bacterial flora:

- E.coli, pneumococci and klebsiella → 80% in the past
- Gram +ve organisms → >50% (with selective intestinal decontamination)
- Anaerobes → only 1% Of cases

2- **Routes of transmission** (Bacterial seeding of ascitic fluid):
    - Translocation of bacteria through the intestinal wall → >70%
    - Hematogenous spread → 50% of cases are accompanied with bacteremia (sometimes the organism cultured from urine or sputum)

3- **Risks for ascitic fluid infection:**
    - A prior episode of SBP: the most important risk factor (2/3 of patients will develop a recurrence within the following year)
    - GIT bleeding (esp. variceal hemorrhage)
    - Ascitic fluid total protein < 1 g/dl

4- **Colonization of ascitic fluid** (bacterascites)
    - Two different outcomes: clearance by intraperitoneal phagocytic cells (opsonization of the bacteria) or progressive bacterial growth with peritonitis (i.e. SBP)

Clinical features

1- Patient with cirrhotic ascites with unexplained marked deterioration should suspect SBP (prompt diagnostic paracentesis)

2- About 87% of patients of SBP have manifestations of infection
    - Fever → 69%
    - Abd. Pain → 59%
    - Mental status change → 54%
    - Rebound tenderness

3- It may be asymptomatic

Diagnosis

1- Diagnostic paracentesis (see table)

2- Lactoferrin : is a product of activated PMNs , and may provide simple and rapid test if it becomes commercially available

3- Leukocyte esterase dipsticks: can detect elevated PMN count in 90-180 sec. at the bedside (in most studies dipstick designated for urine)

Classifications [Types]

Category	Ascitic fluid analysis

Spontaneous bacterial peritonitis	PMNs $\geq 250/ mm^3$, single organism
Culture- negative neutrocytic ascites	PMNs $\geq 250/ mm^3$, negative culture
Monomicrobial non-neutrocytic bacterascites	PMNs $< 250/ mm^3$, single organism
Polymicrobial bacterascites	PMNs $< 250/ mm^3$, multiple organisms
Secondary bacterial peritonitis	PMNs $\geq 250/ mm^3$, multiple organisms

1- SBP (Spontaneous bacterial peritonitis):

- No intra-abdominal surgical source of infection

2- CNNA (Culture- negative neutrocytic ascites):

- No intra-abdominal surgical source of infection
- Most commonly due to suboptimal culture technique [or one dose antibiotic]
- With sensitive culture technique, it represents resolution of transient bacterial colonization of the ascitic fluid because of the fluid's inherent antibacterial properties
- Bacterial growth may continue leading to SBP and positive culture
- Causes of CNNA other than SBP should be considered:
  - Peritoneal carcinomatosis
  - Pancreatitis
  - TB peritonitis
  - Peritonitis related to connective tissue diseases
  - Hemorrhage into ascitic fluid
- TTT : the same as SBP (comparable mortality rates)

3- MNB (Monomicrobial non –neutrocytic bacterascites):

- Variant of SBP with positive culture and normal ascitic PMNs
- When ascitic fluid culture unexpectedly reveals an organism, repeat paracentesis promptly to evaluate for the development of a neutrocytic response which need antibiotic treatment

- TTT: the asymptomatic bacterascites typically resolved spontaneously without antibiotic treatment, while symptomatic bacterascites should be managed as SBP

4- **Polymicrobial bacterascites**

- Indicates inadvertent perforation of the bowel by the paracentesis needle
- Perforation occurs rarely, typically with extremely difficult paracentesis, and may be obvious when air or stool is aspirated during tap.
- Most inadvertent bowel perforations resolve spontaneously without development of 2ry peritonitis; but paracentesis should be repeated to evaluate for a neutrocytic response and the need for antibiotics
- TTT: Antibiotics covering gram negative enteric, gram positive and anaerobic organisms

5- **2ry bacterial peritonitis:**

- Known or suspected surgically treatable intra-abdominal source of infection (e.g. perforated viscus or intra-abdominal abscess)
- Other ascetic fluid findings:
  - Total protein > 1g/dl
  - Glucose < 50mg/dl
  - LDH > the upper limit of normal for serum
- Suspected when: repeat paracentesis after 48hr of appropriate antibiotic treatment reveals PMNs > the baseline value
- TTT:
  - Antibiotics covering gram -ve enteric, gram +ve and anaerobic bacteria
  - Localization of the perforation site
  - Prompt surgical intervention as medical therapy alone is insufficient

Treatment of SBP

1- **Empirical treatment:**

- Indicated before culture when ascetic fluid PMNs ≥ 250cells/mm^3

- The most common organisms: E.coli (43%), streptococcus sp. (23%), klebsiella pneumoniae (11%), rarely anaerobes (except in 2ry peritonitis), fungi (in HIV and 2ry peritonitis)
- Aminoglycosides contraindicated in cirrhotic patients with ascites (nephrotoxicity)

2- **Third generation cephalosporins:** are the recommended treatment

- Cefotaxime: non-nephrotoxic and cover > 94% of the responsible flora
- Dose: 2 gm I.V. / 8 hrs for 5 days
- After one dose → ascitic fluid culture become sterile
- Alternative drugs → amoxicillin-clavulanic acid & fluroquinolones

3- **Specific treatment:** given once culture results become available and the sensitivities of the causative organism are known

4- **Follow up paracentesis if:**

- 2ry bacterial peritonitis is suspected (write criteria ®)
- Typical clinical response to cefotaxime does not occur [fall in serum WBCs, defervescence, -ve culture and ↓ PMN than the pretreatment values] → this means SBP caused by an organism resistant to cefotaxime or 2ry bacterial peritonitis

5- **Intravenous volume expanders:**

- SBP is associated with marked increase in cytokines (TNFα, IL-6) and NO, a potent vasodilator
- These changes → clinical deterioration in B.P, renal function, coagulation and hepatic function
- I.V. volume expanders as albumin ↑ central volume & maintain renal perfusion
- One study reported that administration of I.V. albumin 1.5 g/kg at the time of diagnosis of SBP & 1g /kg on day 3 of antibiotic treatment → decrease risk of renal insufficiency and SBP related mortality

6- **Prophylaxis of ascitic fluid infection**

- Indications:

- High risk for development of SBP [Previous episode of SBP, GIT bleeding, Ascitic fluid total protein < 1g/dl during hospitalization]
- Selective intestinal decontamination to prevent SBP suggested in these situations

Indication for prophylaxis	**Duration of prophylaxis**
Recovery from an episode of SBP	Indefinitely or until ascites disappear
GIT bleeding in cirrhotic patient	7 days
Ascitic fluid protein <1.5g/dl+one of the following: - Child-Turcotte-Pugh score ≥ 9 & bilirubin >3mg/dl - Creatinine ≥ 1.2 mg/dl - BUN ≥ 25mg/dl - Serum Na ≤ 130mEq / L	Continue until decompensated liver disease improves or liver transplantation performed
Ascitic fluid protein < 1 g/dl	During hospitalization (controversial)

- Norfloxacin (400mg once daily) suitable because of:
  - Poor absorption when taken orally
  - Effective against enteric gram –ve organisms (selective intestinal decont.)
  - Sparing of gram +ve and anaerobes to maintain their protective role in the normal gut flora
- Norfloxacin long term prophylaxis leads to:
  - Rapid development of quinolone resistant organisms in the fecal flora
  - Quinolone resistant gram –ve bacilli in 50% of SBP culture
  - High incidence of UTI by quinolone resistant gram –ve bacilli

- Trimethoprim-sulfamethoxazole: reported to be effective in preventing SBP (one double strength tab. orally daily)
- I.V. ceftriaxone: more effective than oral norfloxacin for SBP prophylaxis in patients with advanced cirrhosis and GIT bleeding
- Norfloxacin benefits:
    - ↓ incidence of SBP
    - Delays progression to hepatorenal syndrome
    - Improve overall survival

Risk	Recurrence at 1 year	After norfloxacin
Previous episode of SBP	68%	20%
GIT hemorrhage	45-66%	10-20%
Protein < 1g/dl	20%	0%

VASCULAR LIVER DISEASES

Portal vein thrombosis

Classifications

1- **Acute PVT:**
- Symptoms < 60 days before presentation
- No evidence of underlying cirrhosis or portal HTN on endoscopy or imaging

2- **Chronic PVT:**
- Isolated or as a complication of cirrhosis
- Portal vein collaterals + portal HTN distinguish it from acute PVT

3- **Splenic vein thrombosis:**
- May develop in isolation from thrombosis within the main portal vein
- Leads to splenomegally and isolated gastric varices without esophageal varices

Etiology

1- **Underlying thrombotic disorder:** (in 70% of patients)
- Hematologic disorders

    - Polycythemia rubra vera
    - Myeloproliferative disorder associated with JAK2 mutation V617F
    - Paroxysmal nocturnal hemoglobinuria
    - Antiphospholipid syndrome
- Inherited thrombotic diathesis:
    - Factor V leiden mutation
    - Protein C ↓
    - Protein S ↓ (rare)
    - Antithrombin ↓ (rare)
    - Prothrombin gene mutation (G20210A)
- Pregnancy or high dose estrogen (OCC)
- Chronic infections of the liver
    - Aspergillosis
    - Amebic abscess
    - Hydatid cysts
    - TB
- Tumors:
    - HCC
    - Renal cell carcinoma
    - Leiomyosarcoma
- Chronic inflammatory diseases:
    - Behcet's disease
    - Inflammatory bowel disease
    - Sarcoidosis

2- Abdominal infections resulting from pylephlebitis:

- Acute appendicitis
- Acute cholecystitis or cholangitis
- Pancreatitis

3- PVT in cirrhosis result from combination of:

- Diminished blood flow within the portal vein
- ↓↓ levels of protein C & S
- HCC, either by a procoagulant pathway or by direct invasion of portal vein

4- Isolated thrombosis of the splenic vein following:

- Chronic pancreatitis
- Direct trauma to the abdomen

5- **Miscellaneous:**

- Umbilical sepsis
- Post-operative esp. after splenectomy
- Pancreatic tumors

Clinical features

1- **Acute PVT**

- Abdominal pain and nausea
- Intestinal ischemia: esp. when thrombosis also involves the superior mesenteric vein
- Intestinal infarction: uncommon but fatal

2- **Chronic PVT**

- Gastroesophageal varices
- Splenomegaly
- Thrombocytopenia
- Variceal bleeding (often well tolerated in the absence of cirrhosis)
- Ascites: rare in the absence of cirrhosis & usually early and transient (subsides as the collaterals develop)
- If no cirrhosis → liver is normal in size and consistency

Diagnosis

1- **Doppler U/S** → sensitivity > 70% and specificity > 80%

2- **CT & MRI** → identify thrombus within the portal vein (sensitivity and specificity = 98%) but recanalization of the portal vein may cause problems in interpretation

3- **Liver biochemical test levels** → normal except in patients with underlying chronic liver disease

4- **A thorough evaluation** → for HCC and underlying thrombotic disorders

Treatment

1- **Acute PVT:**

- Anticoagulation with heparin or low MW heparin is indicated
    - May promote recanalization if within the first 30 days
    - ↓↓ risk of complications (as intestinal infarction)
    - If underlying thrombotic disorder → long term anticoagulation
- Thrombolysis: associated with high rate of bleeding
- Surgical thrombectomy: not recommended because of the unacceptable rate of complications except when resection of infracted bowel is required

2- Chronic PVT:

- Long term use of beta-blocker: ↓ risk of variceal bleeding
- Band ligation of varices: safe and effective
- Splenectomy: effective in treatment of gastric varices from isolated splenic vein thrombosis
- Surgical portosystemic shunts: if non-invasive methods of treating varices fail
- Role of long term anticoagulation in patients with underlying cirrhosis
    - Not effective
    - Probably safe if patients carefully selected

Budd - Chiari syndrome

Definition

1- BCS result from obstruction to hepatic venous outflow and may be caused by either thrombotic or non thrombotic occlusion

Classification: according to

1- **The duration of symptoms** and signs of liver disease:

- Acute
- Subacute
- Chronic

2- The site of obstruction

  - Small hepatic veins (excluding terminal venules)
  - Large hepatic veins
  - Hepatic IVC

3- The cause of obstruction:

  - Membranous web
  - Direct infiltration by tumor or metastasis along veins
  - Thrombosis

■ Most of patients present within 3 months of the onset of symptoms

■ Most of patients have subacute or chronic disease at presentation, a finding suggesting that thrombosis of intrahepatic veins leads subsequently to occlusion of large collecting veins

Etiology

1- Membranous occlusion of hepatic veins (MOHV):

  - Is a common cause in Asia, but rarely in USA
  - Many investigators have assumed the webs are congenital, but the onset of symptoms in the 4th decade of life, and the pathologic features are more suggestive of a post-thrombotic event

2- Underlying thrombotic disorder: in most patients with BCS (write)

3- **Idiopathic:** in < 20% of cases

Clinical and laboratory features

1- **The classic triad** of: Tender hepatomegaly + ascites + abdominal pain seen in most patients but not specific

2- **Splenomegaly**: in 50% of patients

3- **LL edema:** with thrombosis or compression of the IVC

4- Negative hepatojugular reflux

5- Jaundice: rare

6- **Portal HTN:** causing death if untreated in > 50%, except in some patients with membranous webs in whom symptoms develop slowly

7- **Ascitic fluid characteristics** useful clues to the diagnosis:

  - High protein conc. > 2gm/dl

- WBC usually < 500/mm^3
- SAAG usually ≥ 1.1

8- Routine biochemical and hematologic parameters: little value (non specific)

9- **DD:**

- Right sided HF
- Constrictive pericarditis
- HCC
- Metastatic disease of the liver
- Alcoholic liver disease
- Granulomatous liver disease

Diagnosis (High index of suspicion)

1- **U/S:** Color flow Doppler U/S is better than duplex U/S which is superior to real time U/S

- Sensitivity, specificity (85%-90%)
- Show low or absent hepatic venous flow
- May show thrombus within hepatic veins

2- **MRI**: with gadolinium contrast or pulsed sequencing

- Sensitivity and specificity → 90%
- Can show thrombus and detect absent hepatic venous blood flow

3- **Three-phase CT:**

- Sensitivity and specificity → 85%-90%
- It can also detect multifocal regenerative nodules (> 2cm) that develop in some patients

4- **Hepatic venography:**

- Unnecessary if findings are noted on noninvasive imaging
- Usually done with TIPS
- Thrombus within hepatic veins
- Spider-web pattern of collateral vessels

- Inability to canulate the hepatic vein orifices

5- **Pathologic findings on liver biopsy specimens:**

- Evidence of high grade venous congestion
- Centrilobular liver cell atrophy
- Thrombi within terminal hepatic venules rarely seen
- Heterogeneous involvement of liver occasionally problematic (sampling error)

6- **The diagnostic approach of suspected hepatic vein occlusion:**

- Should begin with color Doppler U/S
- Followed by three-phase CT or MRI.
- If imaging is equivocal for BCS, then hepatic venography with inferior vena cavography should be done to confirm the diagnosis.
- Liver biopsy may be of value to define the extent of fibrosis but is usually unnecessary

Treatment

1- **Medical treatment:** (provides short term symptomatic benefit)

- Diuretic → to relieve ascites
- Anticoagulation with heparin followed by warfarin
  - Recommended in all patients to prevent repeat thrombosis (< 25% of patients relieving symptoms)
  - Anticoagulation is critical in thrombotic disorders
- Thrombolytic therapy → successful in few reported cases (streptokinase in recent cases????)

2- **Minimally invasive approaches:**

- Rationale
  - Hepatocellular injury may result from microvascular ischemia caused by congestion.
  - Portosystemic shunting → a low-pressure path to decompress the congested liver.

- Angioplasty: of short-segment obstructions (webs or short hepatic vein stenoses)
    - Relief of obstruction is temporary, and repeated treatment is required for long-term management.
    - Placement of a metal stent in the hepatic vein following angioplasty of a short-segment stenosis → improves long-term patency.
    - Placement of a stent in the vena cava → relief of compression from an enlarged caudate lobe of the liver and can be followed by a side-to-side portacaval or mesocaval shunt, if necessary.
- TIPS: can be done in > 90% despite occlusion of hepatic veins.
    - Mortality rate < 2%; complication rates are 15% - 20%.
    - The liver transplant-free 5-year survival rate is approximately 85%.
    - Coated stents have better long-term patency than noncoated stents.
    - Refractory encephalopathy develops in < 10% of patients; it may require liver transplantation.

3- Liver transplantation

- Corrects some underlying clotting disorders and restores hepatocellular function.
- The actuarial 3-year survival rate is 80%, and the 5-year survival rate is approximately 70%; significant improvement in survival in the MELD era.
- Recommended if minimally invasive procedures fail and in selected patients with liver failure or PVT.
- BCS can recur in the post-transplant liver.

4- Transcardiac membranotomy: for membranous obstruction of the IVC and rarely the hepatic veins.

5- **Portosystemic shunt surgery:** now not used because of the high rate of complications, substituted by TIPS but remain an option.

- Side-to-side portacaval shunt
- Mesocaval shunt
- Mesoatrial shunt
- Side-to-side portacaval with cavoatrial shunt

Algorithm for evaluation and management of BCS:

1- **The diagnosis of BCS should be suspected**

- In any patient with ascites and hepatomegaly, particularly if evidence of a thrombotic diathesis is present.
- A high ascitic protein conc.(> 2gm/dl) or high SAAG (≥ 1.1) is a clue to the diagnosis.
- Anticoagulation should be considered in those patients with a defined thrombotic disorder.

2- **Color Doppler or duplex U/S**

- Should be used to visualize the hepatic veins and determine the patency of the IVC.
- If doubt exists, three-phase CT or MRI is indicated.
- If imaging is equivocal for BCS, then hepatic venography with inferior vena cavography should be done to confirm the diagnosis.

3- **If the patient has evidence of hepatic vein outflow obstruction**

- Angioplasty or TIPS should be considered to provide portal decompression.
- An IVC stent can be placed to relieve compression temporarily by an enlarged caudate lobe.
- All patients should undergo early portosystemic decompression

4- **If TIPS fails and cirrhosis is absent**

- Surgical portosystemic shunt surgery should be considered.
- Hepatic venography and vena cavography are required to determine the need for mesoatrial versus mesocaval shunting.

- Mesoatrial shunts are preferable in patients with a high pressure gradient across the hepatic vena cava, provided the surgeon is experienced in this operation.
- If the IVC is patent, mesocaval shunting with or without placement of an IVC stent is possible.

5- **If hepatic decompensation is present or if other interventions fail**

- Liver transplantation is indicated.
- Early portosystemic decompression with TIPS is desirable until a donor organ is available.

Sinusoidal obstruction syndrome (SOS)

Definition and etiology

1- **Acute form:**

- Seen following bone marrow or hemopoietic stem cell transplantation.
- It's thought to result from toxicity of high dose of cyto-reductive therapy with or without hepatic irradiation

2- **Chronic form:**

- It results from toxicity of pyrrolizidine alkaloids from plants Crotalaria, senecio, and Heliotropium ingested in the form of herbal teas hence the term Jamaican bush tea disease

Clinical features

1- **Acute form:** occurrence of ≥ 2 of the followings within 20 days after bone marrow transplantation

- Painful hepatomegaly
- Sudden weight gain > 2% of baseline body weight
- Total serum bilirubin > 2 mg/dl

2- **Chronic form:** is similar to BCS

- Tender hepatomegaly
- Ascites
- Abdominal pain

Diagnosis

1- **CT** may be helpful in distinguishing SOS for graft-versus-host (GVH) disease

- Patients with SOS have:
  - Periportal edema
  - Ascites
  - Narrow right hepatic vein
- Patients with GVH disease:
  - Often have thickening of small bowel

2- **Liver biopsy:**

- Usually shows sinusoidal and perivenular fibrosis as well as subendothelial sclerosis

Treatment

1- **Treatment of SOS following bone marrow transplantation**: is largely supportive

- Fluid support
- Platelet & red blood cell transfusion is often necessary due to profound cytopenia accompanying bone marrow transplantation
- Dopamine and other pressors to maintain renal perfusion
- Broad-spectrum antibiotics to treat presumptive infection

2- **Defibrotide:**

- May be of benefit in treating severe SOS with a complete remission rate of 30-60%.

3- **Chronic SOS associated with ingestion of pyrrolizidine alkaloids:**
   - Often require liver transplantation due to extensive fibrosis that is usually present at time of diagnosis

4- **TIPS** has been of benefit in as small number of cases

5- **Antithrombin:**
   - May be of benefit in preventing progression of SOS if given early in the course of illness

6- **Drugs with limited success** in preventing SOS include:
   - Prostaglandin E
   - Uesodeoxycholic acid
   - Pentoxyphylline
   - Heparin

HEPATIC ABSCESSES & CYSTS

Amoebic liver abscess

Pathogenesis

1- **Organism** → E.histolytica

2- **Infective stage** → cyst

3- **Mode of transmission** → fecal-oral rout

4- **Infection:** excystation occurs in the Small intestine → the trophozoite infect the colon

5- **Formation of amebic abscess:**

- In the liver, E.histolytica lyses the host's tissue with proteolytic enzymes leading to multiple small cavities which coalesce forming the abscess
- The hepatic lesion is a well demarcated abscess usually in the right lobe (by the streaming effect) and consisting of:
    - Necrotic liver tissue
    - Acellular debris, RBCs and leucocytes
    - Amebic trophozoites only at the periphery and can invade further

6- **Host factors** contribute to the severity of the disease:

- Age (children > adults)
- Pregnancy
- Malnutrition
- Alcoholism
- Corticosteroid
- Malignancy

Clinical features

1- **Onset** is insidious

2- Amebic liver abscess manifests with **amebic colitis** in only 10% of cases

3- 20% have past **history of diarrhea or dysentery**

4- E. histolytica **isolated from the stool** in approximately 50% of cases

5- **History:** [socioeconomic and demographic]

- Emigrant from or resident in an endemic area
- Traveler to an endemic area
- Men > women (3 - 10 times)
- Young adults > children or elderly persons

6- **Symptoms**

- Fever, rigors, night sweats
- Nausea, anorexia, malaise
- Right upper quadrant abdominal discomfort or severe pain
- Weight loss
- Chest symptoms: dry cough, pleuritic pain
- Diaphragmatic irritation: shoulder tip pain, hiccups

7- **Physical examination**

- Fever
- Tender hepatomegaly ± cystic mass
- Chest signs: dull right base (usually from raised hemidiaphragm); crackles at right base; pleural rub
- Jaundice and peritonitis or pericardial rub: rare; poor prognostic signs
- Intercostal tenderness and tender fist percussion

Diagnosis

1- Laboratory findings

- Increased serum bilirubin level is uncommon

Laboratory finding	Frequency (%)
Leukocytosis	80%
↑ serum alkaline phosphatase level	80%
Anemia	>50%
↑ ESR	Common
Proteinuria	Common
↑ ALT, AST	Poor prognostic sign

2- Diagnostic imaging

- Chest X ray:
  - Elevation of right hemidiaphragm
  - Blunting of right costophrenic angle
  - Atelectasis
- U/S:
  - Round or oval single lesion (sometimes multiple)
  - Lack of significant wall echoes, so the transition from abscess to normal liver is abrupt
  - Hypoechoeic appearance compared with normal liver; diffuse echoes throughout abscess
  - Peripheral location, close to liver capsule
  - Distal enhancement
- CT:
  - Well-defined lesions, round or oval, mostly single (may be multiple)
  - Low density compared with surrounding liver tissue
  - Nonhomogeneous internal structure

- MRI:
    - Abscess characterized by low signal intensity on T1-weighted images
    - High signal intensity on T2-weighted images
- Radionuclide imaging:
    - Cold spot distinguishing it from pyogenic abscess

3- Serologic tests:

- ■ Detection of antibodies is the mainstay of diagnosis of invasive Amebiasis
- ■ Positive serologic tests are found in 95% to 100% of patients with amebic liver abscess
- ■ These tests are positive in all forms of invasive amebic disease (including dysentery). So, combined testing may be necessary for accurate diagnosis

- Indirect hemagglutination
    - Sensitivity of 90% to 100%
    - Raised titers may persist for more than 2 years
- Latex agglutination → Rapid results
- Indirect immunofluorescence → Positivity may persist > 6 months
- Gel diffusion → Useful for differentiating recent from past infection because result remains positive for only 6 to 12 months after the onset of infection
- Counterimmunoelectrophoresis → Cellulose acetate precipitation test (CAP) is highly sensitive and specific; becomes negative quickly after successful treatment; regarded as a reference test for amebic serology
- Complement fixation → +ve
- Enzyme-linked immunosorbent assay
    - Sensitivity and specificity as high as 97.9% and 94.8%, respectively

4- Aspiration of abscess (when diagnosis is uncertain or for imminent rupture)

- Yellow to dark brown “anchovy sauce”

- Odorless
- "Pus" consisting mainly of acellular debris; most amebae found in abscess wall

Complications

1- **Rupture of abscess into the following:**
  - Chest, causing
    - Hepatobronchial fistula (± expectoration of "anchovy" pus)
    - Lung abscess
    - Amebic empyema (right pleural effusion)
  - Pericardium, causing
    - Heart failure
    - Pericarditis (in right lobe abscess)
    - Cardiac tamponade (often fatal; may be followed by constrictive pericarditis)
  - Peritoneum, causing
    - Peritonitis
    - Ascites
  - Skin

2- **Secondary infection** is usually iatrogenic following aspiration

3- **Other complications** (rare):
  - Fulminant hepatic failure
  - Hemobilia
  - Inferior vena cava obstruction
  - Budd–Chiari syndrome
  - Hematogenous spread causing cerebral abscess

4- **Factors predisposing to complications:**
  - Age > 40 years
  - Concomitant corticosteroid use
  - Multiple abscesses
  - Large abscess > 10 cm in diameter
  - ESR and CRP marked elevation

Treatment [Usually with drugs alone]

1- **Commonly used regimens** (administered orally):
  - **Metronidazole** 750 mg 3 times daily for 5 - 10 days (pediatric, 35 - 50 mg/kg per day in 3 divided doses for 5 days), or
  - **Tinidazole** 2 g/day for 3 days, (pediatric, 50 - 60 mg/kg daily for 5 days) or
  - **Chloroquine** 1 g loading dose for 1 - 2 days, then 500 mg/day for 20 days (pediatric, 10 mg/kg base).

2- **Luminal amebicides** (must used following the aforementionedRegimens):
  - **Diloxanide furoate** 500 mg 3 times daily for 10 days (pediatric, 20 mg/kg per day in 3 divided doses), or
  - **Diiodohydroxyquin** 650 mg 3 times daily for 20 days (pediatric, 30 to 40 mg/kg per day in 3 divided doses; maximum 2 g/day), or
  - **Paromomycin sulfate** 25 to 35 mg/kg/day in 3 divided doses for 5 - 10 days (pediatric, 25 to 35 mg/kg per day in 3 divided doses)

3- **Optimal management**
  - Patients with suspected amebic abscess should be started on therapy while awaiting serologic confirmation.
  - Response is usually rapid, with defervescence occurring in 48 - 72 hours
  - Indications for radiologically guided fine-needle **aspiration** [to avoid rupture and to exclude a pyogenic abscess]:
    - Critically ill patients
    - Those with left lobe abscess
    - Those who do not respond to initial drug therapy
    - Impending rupture

4- **Complications:** such as rupture of the abscess may be managed medically but often require percutaneous drainage. Surgical drainage is seldom required

Prognosis

1- Amebic liver abscess is an eminently **treatable condition**

2- The **mortality rate is < 1%** in uncomplicated disease

3- Delay in diagnosis may result in **abscess rupture**, with a higher mortality rate:

- Rupture into chest or peritoneum: 20% mortality rate
- Rupture into pericardium: 32% - 100% mortality rate

Hepatic hydatid cyst

Pathogenesis

1- **The causative pathogen:** Echinococcus granulosus (tapeworm).

2- **Intermediate host:** dogs, becomes infected by eating the viscera of infected sheep that contain hydatid cysts and excrete Echinococcus eggs in feces

3- **Mode of transmission:** Eggs are ingested by humans, either from contamination of soil and foodstuffs or from the dog's coat

4- **Formation of the cyst:**

- Eggs hatch in the intestine to form oncospheres that invade tissue to enter the portal circulation.
- Each oncosphere matures into a vesicle and subsequently a cyst, the metacestode and results in hepatic disease in 50% to 70% of cases.
- Other sites of disease are as follows:
    - Lung (20% to 30%)
    - Bone (less than 10%)
    - Brain and heart
- Cysts consist of a germinal layer that buds asexually to form daughter cysts, which contain protoscolices, the infective forms that are ingested by the definitive host
- Cysts enlarge slowly and cause tissue damage directly or by compromising the blood supply. The parasite causes a host response to form a collagenous capsule around the germinal layer. This capsule may calcify. Often, no host inflammatory response occurs.

5- **Risk factors:**

- A case-control study conducted in Spain found that long-term coexistence with dogs is a major risk factor for the development of E.

granulosus infection, especially coexistence with dogs with the opportunity to eat potentially infected offal.

Clinical features

1- Symptoms

- Cysts may be asymptomatic and often become symptomatic only after decades, because of their slow growth. Symptoms are caused by pressure effects.
- Symptoms may follow cyst rupture or leakage
- The presentation of a secondary infection of a hydatid cyst resembles the presentation of a pyogenic abscess ®.

2- Physical examination

- Tender mass
- Chest signs, especially at the right base
- Fever
- Jaundice

Clinical features of 650 patients with a liver hydatid cyst

Feature	**Number (%)**
Abdominal pain	66.9%
Fullness in the upper abdomen and dyspepsia	36%
Hepatomegaly	30%
Asymptomatic	28%
Jaundice	16%
Mass in the right upper quadrant	6%
Acute abdomen	2%

Diagnosis

1- **Laboratory findings**
   - ↑ serum alkaline phosphatase level
   - Peripheral eosinophilia (>7%) in 30% of patients, usually indicating leakage or rupture of cyst
   - ↑ serum bilirubin level (uncommon)

2- **Diagnostic imaging**
   - Chest x-ray
     - Elevation of the right hemidiaphragm
     - Cysts may be visible in the lung
     - Calcification of hepatic cyst may be visible below the diaphragm
   - Ultrasonography
     - Cysts may be anechoic
     - Typically round
     - Septate or daughter cysts are often visible
     - Separation of germinal membrane: "water-lily sign"
     - Collapsed cysts may be visible
     - Calcification of wall
     - Hydatid "sand"
   - CT
     - Germinal layer seen clearly
     - Daughter cysts readily visualized
     - Lesion of low attenuation: 3 to 30 Hounsfield units
   - MRI
     - Characteristic low-intensity rim 4 - 5 mm thick, best seen on T2-weighted images
     - Lesion center nonhomogeneous
     - Lesion is hypointense on T1-weighted images, hyperintense on T2-weighted images

3- **Serologic tests:**

- Indirect haemagglutination (IHA) and ELISA are 75% - 94% sensitive
- Specificity is lower, necessitating a confirmatory test (e.g., molecular biologic methods or immunoblotting).

4- **Molecular biologic tests:** PCR–derived probes allow diagnosis and species differentiation.

Complications

1- **Leakage or rupture** of cyst (sometimes iatrogenic from aspiration of undiagnosed hydatid cyst) may result in the following:

- Allergic reaction, including anaphylaxis (may be fatal)
- Dissemination of disease
- Cholangitis if cyst ruptures into the biliary tract
- Hemoptysis and secondary infection if bronchial rupture

2- **Secondary infection** of cyst behaves like a pyogenic abscess

Treatment

1- **Surgery remains the mainstay of treatment**

- The combination of surgery with chemotherapy is the safest and most effective approach
- Secondary infection should be treated as pyogenic abscesses; however, aspiration of an infected hydatid cyst is more hazardous than is aspiration of a pyogenic abscess ®.

2- **Drug therapy:**

- **Albendazole** 10 - 14 mg/kg/day orally for 3 months initially (may continue for1 year) or
- **Mebendazole** 30 - 70 mg/kg/day orally for 3 months (may require up to 200 mg/kg per day)
    - These benzimidazole agents act on the germinal layer
- **Praziquantel** (40 mg/kg orally per day for 14 days) has been used as a protoscolicide and, as such, has an important role preoperatively

3- **Surgical and radiologic options:**

- The technique chosen depends on the condition of the patient, characteristics of the cyst, and experience of the surgeon or radiologist
- Radical surgery: pericystectomy or hepatic resection
- Conservative surgical treatment through unroofing and management of the residual cavity
- Laparoscopic procedures
- Percutaneous techniques, including puncture, aspiration, injection, reaspiration (PAIR)

4- **Complications of surgery:**

- The complication rate of surgery may be **high**
- For example, 57% in a series of 59 patients had dissemination of infection, secondary infection, fistula formation, or complications from seepage of scolicidal agents into the biliary tract (causing a syndrome resembling sclerosing cholangitis).

Prognosis

1- Hydatid cysts may remain asymptomatic throughout a person’s life

2- Cyst rupture or infection is associated with considerable mortality

Pyogenic liver abscess

Incidence

1- Pyogenic liver abscess is rare; population-based studies report 11 cases per million per year

Risk factors

1- Liver abscess often occurs in patients with a predisposing medical condition:

- Biliary disease
- Hypertension
- Malignant disease
- Diabetes mellitus
- Previous abdominal surgery or endoscopic procedure

- Cardiovascular disease
- Crohn’s disease
- Diverticulitis
- History of trauma

Pathogenesis

1- **Source of infection:**

- Blood stream or bile
- Frequently, no infective source is found (cryptogenic liver abscess)
- However, when one can be identified, common sources include the following:
    - Cholangitis, secondary to biliary stricture, stones, or endoscopic intervention
    - Intra-abdominal sepsis (e.g., diverticulitis, peritonitis)
    - Generalized septicemia
    - Dental infection
    - Trauma, including liver biopsy or surgery
    - 2ry infection of a preexisting liver cyst, neoplasm (including after ablative therapy), or rarely an amebic abscess

2- **Causative organisms**

- Cultures of blood or abscess contents are positive in most cases
- Lesions are often polymicrobial
- The most common is Klebsiella species (particularly Klebsiella pneumoniae) then E. coli
- Microaerophilic organisms, particularly *Streptococcus milleri,* are increasingly common causes but need careful cultivation to isolate
- Anaerobic organisms are commonly isolated from polymicrobial abscesses
- Unusual organisms include *Salmonella, Haemophilus,* and *Yersinia* spp. Tuberculosis, actinomycosis, and melioidosis also occur, especially in

patients with defective immunity (e.g., HIV infection, post-transplantation status).

3- The right lobe of the liver is the most frequently involved

4- Abscesses may be single or multiple; those caused by hematogenous spread are frequently multiple

5- The abscess contains
   - Polymorphonuclear neutrophils
   - Necrotic liver cells surrounded by a fibrous capsule

Clinical features

1- **Age :** More common in middle-aged and older people

2- **History** [Presenting symptoms found in a retrospective study of 79 patients with pyogenic liver abscess]

Symptom	Frequency (%)
Fever	89.6
Right upper quadrant pain	72.2
Chills	69
Nausea	43.1
Vomiting	32.3
Weight loss	26.1
Jaundice	21.4
Headache	17.5
Myalgias	11.9
Diarrhea	10.7

3- **Physical examination**
   - Fever
   - Finger clubbing (rare)
   - Jaundice (in 33%)
   - Tender hepatomegaly
   - Classic triad of fever, jaundice, and tender hepatomegaly found in less than 10% of patients

Diagnosis

1- **Laboratory findings**

Feature	**Frequency (%)**
Increased ESR	100
Leukocytosis	75
Anemia	50
Elevated serum bilirubin level	Common
Elevated ALP	Common
Increased ALT/AST	Common
Prolonged PT	Common
Decreased serum albumin level	Poor prognostic sign

2- Diagnostic imaging

- Chest radiograph abnormal in 50%:
    - Elevation of right hemidiaphragm
    - Blunting of right costophrenic angle
    - Atelectasis
    - If a gas-forming organism is the cause of abscess, fluid levels may be visible below the diaphragm
- U/S
    - Round, oval, or elliptoid lesion
    - Irregular margin
    - Hypoechoic with variable internal echoes
- CT
    - Highly sensitive; detects up to 94% of lesions
    - Lesions show reduced attenuation and possibly enhance with contrast
- MRI
    - More sensitive at detecting small lesions than CT
    - Lesions have low signal intensity on T1-weighted images and very high signal intensity on T2-images; lesions enhance with gadolinium
- Radioisotope study
    - Gallium is avidly taken up by abscesses

3- Microbiology

- Blood cultures should be taken before initiation of antibiotic therapy
- Positive blood cultures occur in 50% - 100%.

- Aspiration of the abscess increases the yield of a positive microbiologic diagnosis
- In polymicrobial abscesses, all the causative organisms may not be present in the blood

Complications

1- Septicemia
2- Metastatic abscess
3- Septic shock
4- Acute respiratory distress syndrome
5- Renal failure
6- Rupture

Treatment

1- **In the past**, standard treatment involved open surgical drainage of the abscess in combination with broad-spectrum antibiotics. Studies since the 1990s have shown improved results with either percutaneous drainage or aspiration in combination with antibiotics. Some patients can be managed medically without surgery or aspiration.

2- It is usually possible to **combine diagnostic and therapeutic aspiration** in these patients

3- **Complications of drainage** include:

- Hemorrhage
- Perforation of a viscus
- Infection from the drain
- Catheter displacement

4- **Antibiotic therapy** should include coverage against gram-negative organisms as well as microaerophilic and anaerobic organisms. Empiric first-line regimens are as follows:

- Suspected biliary source: ampicillin + gentamicin + metronidazole
- Suspected colonic source: third-generation cephalosporin + metronidazole

5- **Antibiotic therapy:**

- Usually I.V. initially
- The duration of I.V. antibiotic therapy and the decision to change to oral therapy depends on the clinical response
- Recommended duration of therapy is 2 - 3 weeks

6- **Surgical intervention** may be required if the patient fails to respond rapidly to therapy (flexible approach)

Prognosis

1- Untreated pyogenic liver abscess has a mortality rate approaching 100%.

2- Case series in the 2000s have reported mortality rates as low as 2.5% but usually 10% - 30%, depending on the underlying cause of the abscess and associated medical conditions

3- Improved mortality rates result from advanced imaging and diagnostic techniques and the use of percutaneous drainage

Cystic lesions of the liver

Causes of cystic lesions in the liver

1- **Congenital**

- Infantile polycystic disease
  - Rare autosomal recessive condition that results in cyst formation in the liver and kidneys
  - Hepatomegaly is often present at birth
  - Renal damage is usually the cause of reduced life span
- Adult polycystic disease:
  - Autosomal dominant condition predominantly affecting the kidneys but with hepatic cysts in 33% of patients
  - It is rarely associated with liver dysfunction
  - Treatment should be considered only in the presence of symptoms

- Optimal management depends on cyst morphology, severity of cystic disease, comorbidity, and recurrence rates
- Options include cyst unroofing, liver resection, and, for those with end-stage disease, liver transplantation.

- Choledochal cysts
  - Many disease entities manifest with cystic dilatation of the biliary tract
  - Caroli's disease is one of these conditions in which nonobstructive dilatation of intrahepatic bile ducts occurs

2- **Acquired**

- Benign tumors (e.g., hamartomas)
- Simple cysts
  - Most are small and incidental.
  - Treatment is indicated only for symptomatic cysts:

    Aspiration combined with sclerosis

    Open surgery

    Laparoscopic cyst unroofing, which is considered to be the optimal standard of care
- Infective, most commonly hydatid disease (caused by Echinococcus granulosus)

A diagnostic approach to distinguishing liver abscesses from cysts

1- **Key features include the following:**

- Important clues are found with careful history
- The geographic history is of vital importance

2- **Serological tests and blood cultures**

- Serologic tests are positive in 90% - 100% of cases of amebic liver abscess
- Serologic tests are positive in 75% - 95% of cases of hepatic hydatid disease

- Blood cultures should be done to all febrile patients; amebic and hydatid cavities may become superinfected
- Blood cultures alone are positive in at least 50% of patients with a pyogenic liver abscess

3- **Imaging**

- Confirms the diagnosis of a cyst or abscess
- U/S is the investigation of choice because of high sensitivity, lack of radiation, low cost, and ready availability
- CT may provide further information, especially in pyogenic liver abscess (contrast enhanced) and hydatid disease
- MRI may be more sensitive than U/S and CT for detecting small lesions

4- **Aspiration**

- This is required for diagnosis and treatment in cases of suspected pyogenic abscess
- It gives a microbiologic diagnosis in > 80% of patients with pyogenic abscess
- Combined aspiration and blood cultures positively identify the causative organism in > 85% of cases
- It may be performed in cases of suspected amebic abscess if the abscess is large and rupture is imminent or if the diagnosis is in doubt. Usually, aspiration is not required for diagnosis
- Aspiration should not be carried out in cases of suspected hydatid disease. It may be indicated if the cyst appears to be infected. In the event of aspiration of a hydatid cyst, efforts should be taken to prevent leakage of cyst contents, which has potentially serious sequelae
- Aspiration should be performed by an experienced operator under imaging guidance through as thick a rim of normal liver as possible

Comparison of amebic and pyogenic liver abscess and hydatid cyst

Parameter	Amebic abscess	Pyogenic abscess	Hydatid cyst
Age	Any, mostly younger	Any, mostly older	Any, mostly older
Sex	Male > female	Equal	Equal
Epidemiologic features	Residence or travel in endemic area; poverty, poor hygiene	None; occasional association with helminth Infection	Residence in endemic area; farm animal exposure
Associated medical Conditions	Rare	Common (e.g., surgery; biliary tract disease; diverticulitis)	Rare
Significant jaundice	Rare	Common	Rare
Multiple abscesses (cysts)	Infrequent	Common	Septate and daughter cysts
Liver biochemical tests	Mildly abnormal	More markedly abnormal	Mildly abnormal
Amebic serology	Positive	Negative	Negative
Hydatid serology	Negative	Negative	Positive
Blood cultures	Negative; positive result indicates superinfection	Frequently positive	Negative; positive result indicates superinfection
Abscess contents	Thick fluid; variable color, yellow-brown, odorless	Pus; creamy yellow, foul Smelling	Aspiration not recommended; thin fluid
Effectiveness of medical therapy	Almost always	Often	Usually in combination with surgery
Surgery required	Hardly ever	Sometimes	Usually

Pulmonary vascular complications of liver disease

Hepatopulmonary syndrome

Definition

1- This syndrome is defined as the triad of **cirrhosis with portal hypertension** + **arterial hypoxemia** (Po2 < 70 mm Hg) – increased alveolar–arterial gradient while breathing room air- + **intrapulmonary vasodilatation**

2- HPS causes hypoxemia due to pulmonary VD and arteriovenous shunting

Prevalence in cirrhotics: 5% - 50%

Clinical picture

1. **Dyspnea** of insidious onset (NPV = 100%) , platypnea and orthodeoxia
2. **Cyanosis** : in 90% of cases
3. **Digital clubbing** : PPV = 75%
4. **Spider nevi**: common clinical feature with significant relationship between cutaneous spider angiomata and systemic and pulmonary vasodilatation suggesting that spider nevi may represent a cutaneous marker for intrapulmonary vascular dilatations
5. **Severe hypoxemia** (PO2 < 80 mm Hg, and often < 60 mm Hg)

Types of HPS

1. **Type 1 :** associated with vascular dilatations at the precapillary level close to the normal gas exchange units of the lung
2. **Type II:** associated with focal larger dilatations amounting to AVS distant from the gas exchange units
3. Supplementary oxygen improves type 1 HPS but not type 2 HPS

Diagnostic flow chart of HPS

1- **Arterial blood gas analysis:** performed in the supine position, identify hypoxemia (Po2 < 70 mm Hg) or elevated alveolar-arterial differences in O_2

2- **CXR:**

- Shows bibasilar nodular or reticulonodular opacities in 5-13.8% of patients with CLD and 46-100% of patients with HPS
- Follows to rule out causes of hypoxemia in a cirrhotic patient other than HPS
  - Pulmonary atelectasis
  - Ascites
  - COPD
  - Hepatic hydrothorax

3- **Pulmonary function tests:**

- Spirometry is generally normal but may show a mild restrictive pattern due to pleural effusion or ascites
- DLCO depicts decreased diffusion ability of lungs due to intrapulmonary vasodilatation

4- **99mTc-MMA perfusion scanning** (technetium-99m (99mTc)–macroaggregated albumin scanning):

- Demonstrate intrapulmonary shunting
- Demonstration of AV shunting despite the presence of other cardiopulmonary abnormalities by radiological means can achieve the diagnosis of HPS
- Quantification of AVS is an important consideration when considering patients for LT and Yttrium-90 microsphere embolization for HCC
- In patients with right to left shunt → >6% uptake of the isotope shown in the brain (normally, 5%)
- It allows quantification of the degree of intrapulmonary shunting but unable to differentiate intracardiac from intrapulmonary shunt

  - 99mTc-MMA >20 mm in diameter are entrapped in pulmonary vasculature and undergo decay

5- **Contrast ("bubble") echocardiography (CEE):** demonstrate intrapulmonary shunting

  - In HPS, the microbubbles are usually seen in the left heart after the third heart beat
  - Normally, in intracardiac right to left shunt, the microbubbles are seen in the left heart within the first three cardiac cycles
  - There is maximal left atrial volume ≥50 ml in a cirrhotic patient

6- **CT scan:**

  - Reserved for patients when pulmonary AVM is suspected as the cause of AV shunt
  - But may be performed to look at the liver when the chest can be included into the protocol
  - Identify decreased bronchoarterial ratio, which is highly specific for HPS
  - Excluding pulmonary fibrosis or emphysema as the cause of these opacities (dilated lung vessels)

7- **Pulmonary angiogram:**

  - Is carried out as a prelude to vascular intervention when CT angiography has demonstrated a pulmonary AVM
  - Differentiate between Type I and II HPS. Type I HPS is depicted as normal to advanced diffuse 'spider-like' or spongy appearance

8- **Administration of 100% oxygen** can be used as a noninvasive test to quantify pulmonary AVS:

  - This is an important parameter to measure as demonstration of AVS suggests that the hypoxemia may not resolve following LT
  - In response to breathing 100% oxygen
    - If the PO_2 levels rise to ≥ 600 mmHg, the presence of AVS is unlikely

- If levels fail to exceed 500 mmHg, the presence of a shunt cannot be ruled out
- If PO_2 levels fail to rise to above 150-200 mmHg, shunt is most probably the main mechanism of hypoxemia

Treatment

1- **No effective medical treatment** is available, but better knowledge of the pathophysiology should improve this situation in the future

2- **Liver transplantation:** is the only definitive treatment

3- **Temporizing measures** until LT is performed include

- Medical management
- TIPS
- pulmonary arterial coil embolization

4- Several therapeutic **trials** in HPS have shown poor results such as:

- Somatostatin analogues
- Cyclooxygenase inhibitors
- Immunosuppressive agents (corticosteroids and cyclophosphamide).

5- Almitrine bismesylate:

- Selective pulmonary vasoconstrictor has achieved anecdotal success.

6- Inhaled prostanoid iloprost:

- Could improve quality of life in patients with HPS waiting for LT and post-surgery until the resolution of the hypoxemia

7- A small study using **garlic (*Allium sativum*) powder capsules** daily for a minimum of 6 months:

- Resulted in a modest improvement in arterial oxygenation in 6 out of 15 patients with HPS

8- **Suprahepatic inferior vena cava obstruction** in association with HPS

- Responds to percutaneous balloon cavaloplasty experiencing intrapulmonary shunt reversal.

Prognosis

1- This syndrome is associated with a significantly **increased risk of mortality** without liver transplantation; the risk of mortality increases with the degree of hypoxemia

2- **MELD exception points** may be given to patients with significant hypoxemia (Po2 < 60 mm Hg).

3- **Complete resolution** typically follows liver transplantation, time course of improvement variable and often delayed up to 1 year. However, patients with HPS undergoing LT have a significant mortality of 71% at 1 year

4- The leading **cause of death** is hemorrhagic shock secondary to gastrointestinal bleeding

Portopulmonary hypertension

Definition

1- This is **characterized by** the presence of
  - Cirrhosis with portal hypertension
  - Elevated mean pulmonary arterial pressure (>25 mmHg at rest)
  - Elevated pulmonary vascular resistance (> 240 dynes/second/cm5)
  - Normal pulmonary capillary wedge pressure (<15 mmHg) or an elevated transpulmonary gradient

2- **Right heart catheterization** is required for diagnosis

Clinical features

1- Early stage :
  - Asymptomatic or symptoms of the underlying liver disease
  - A high index of suspicion and screen for PH are needed for diagnosis

2- Advancing disease:
  - Exertional dyspnea: is the most frequent symptom (81%)
  - Other symptoms, such as syncope, chest pain, and fatigue: are seen in 1/3 of the patients.

3- Auscultation:

- May reveal an accentuated pulmonary component of the second heart sound and a systolic murmur

4- **Hemodynamic findings:**

- Included severe pulmonary hypertension with normal pulmonary capillary wedge pressure and cardiac output

Diagnosis

1- **Lung function tests:**

- Not generally helpful although diffusing capacity may be reduced

2- **B-type natriuretic peptide testing:**

- Helpful in monitoring the severity of disease and the efficacy of treatment in PH; but its role in PPH has not been defined

3- **EKG findings in PPH:**

- Right atrial or ventricular enlargement
- Right bundle branch pattern

4- **CXR**

- May be normal in the early stages.
- May show prominent central pulmonary arteries and cardiomegaly (RV) and tapering of the peripheral vessels in advance PH.

5- **Standard echocardiography:**

- Is an excellent tool to detect signs of PH
- Findings suggestive of PPH include elevation of right ventricular systolic pressure (RVSP).
- Patients with an estimated RVSP greater than 50 mmHg undergo right heart catheterization

6- **Right heart catheterization (RHC):**

- Regarded as a definitive test for confirmation of PPH
- Allows accurate measurement of pulmonary artery pressures, pulmonary artery occlusion pressure, cardiac output, and pulmonary vascular resistance.
- RHC has the advantage of excluding other treatable causes of PH

7- **CT scan**

- PH can be diagnosed when the diameter of the main pulmonary artery ≥ 29 mm accompanied by a segmental artery-to-bronchus ratio > 1:1 in 3 of 4 pulmonary lobes or/and the ratio of the main pulmonary artery diameter to the aortic diameter is > 1, particularly in patients < 50 years of age

8- **HRCT :**

- May show a mosaic pattern of lung attenuation [nonspecific finding common to all types for PH but is relatively specific for thromboembolic PH]

9- **Radionuclide lung perfusion scans:**

- May be normal or show diffuse patchy perfusion defects in severe PH

Treatment

1- **Mild PPH**

- Generally not treated [pulmonary artery pressure <35 mmHg]

2- **Moderate-to-severe PPH** attempts are made to improve symptoms and lower pulmonary artery pressures and pulmonary vascular resistance

- Vasodilators:
    - All affected patients should be considered for vasodilator therapy
    - Prostanoids have been used successfully to lower pulmonary pressures in PPH
    - Epoprostenol has short half-life, a complicated delivery regime and is associated with several complications but has been shown to improve exercise capacity in PPH
    - Iloprost has similar effect and is used by inhalation but is very short-acting
    - Bosentan is an endothelin receptor blocker, which is approved by FDA for the treatment of PH and PPH but is associated with mild hepatic dysfunction

- Ambrisentan has recently been approved for the treatment of PH, Mild hepatic dysfunction may occur
- Sildenafil has been shown to increase cardiac output and decrease pulmonary artery pressures and pulmonary vascular resistance without serious adverse events in PH

- Anticoagulant therapy:
  - Not considered because of gastroesophageal varices and coagulation abnormalities related to liver disease
  - But anticoagulation should be considered in the absence of contraindications
- Diuretics:
  - Provide standard therapy in patients with PH and PPH, for the underlying liver disease, especially if ascites or peripheral edema is present
- Oxygen therapy: is used to treat hypoxemia
- β-Blockers:
  - Are used in some patients as prophylaxis of variceal bleeding. However, the use of β-Blockers in PPH is controversial as a significant worsening of exercise capacity has been reported after its use

3- Liver transplantation:

- Not the treatment of choice for PPH, but after optimal hemodynamic and clinical improvement with medical therapy, LT can be considered an option in selected patients
- Contraindicated if mean pulmonary artery pressures > 50 mm Hg
- Patients with mean pulmonary artery pressure between 35 and 50 mm Hg also have an increased mortality rate but may benefit from prolonged treatment for PH.
- Sildenafil use to treat PPH prior to LT has met with some success

Prognosis

1- This disorder is associated with an **increased mortality risk** of up to 50% at 1 year

2- Elevated mean pulmonary artery pressure > 35 mm Hg is associated with increased perioperative mortality and is a contraindication to liver transplantation. So, **screening for PPH is mandatory** in patients undergoing evaluation for LT

Acute kidney injury in cirrhosis

Causes

1- Hepatorenal syndrome

2- Acute tubular necrosis

- This is characterized by an **abrupt impairment** in renal function
- **Predisposing factors** in cirrhotic patients include:
  - Hypovolemic or septic shock
  - Major surgical procedures
  - Exposure to nephrotoxic drugs
- Although no specific markers for ATN have been described, the presence of the following **criteria** may be useful for diagnosis:
  - High urine sodium concentration
  - Urine/serum osmolality ratio < 1
  - Abnormal urine sediment, with epithelial cells and casts

3- Glomerular disease

- Despite the high incidence of glomerular abnormalities on histologic examination of kidney in patients with cirrhosis, signs or symptoms of glomerular dysfunction **seldom develop**

- The presence of glomerular abnormalities seems to be independent of the origin of cirrhosis
- Patients with more severe glomerular abnormalities develop mainly **proteinuria and/or hematuria**

4- Drug induced kidney injury

- **The most common drugs** inducing renal failure in cirrhotic patients include:
  - Aminoglycosides
  - NSAIDs
- Drug-induced renal failure has a clinical profile similar to that of **ATN**

5- Prerenal azotemia

- **Intravascular volume depletion** can lead to prerenal azotemia
- **Causes** of intravascular volume depletion include:
  - Vomiting
  - Diarrhea
  - Diuretic overuse
- **Differentiation between prerenal azotemia and HRS:**
  - It is difficult to differentiate prerenal azotemia from HRS based on urinary sodium or urinary volume; thus these parameters were removed from the diagnostic criteria of HRS
  - Improvement in renal function after albumin expansion allows the differentiation of prerenal azotemia from HRS
  - A negative response to albumin expansion is a major diagnostic criterion of HRS

Hepatorenal syndrome

Definition

1- **Renal failure** (serum creatinine > 1.5 mg/dL) in a patient with **advanced liver** disease and portal hypertension

2- HRS characterized by:

- Marked ↓ in GFR and renal plasma flow (RPF) in the absence of other identifiable causes of renal failure
- Marked abnormalities in systemic hemodynamics
- Activation of endogenous vasoactive systems

Diagnosis

1- Marked **reduction in GFR + exclusion** of other types of renal failure

2- In 2007, the International Ascites Club defined the **diagnostic criteria of HRS**

- Cirrhosis with ascites
- Serum creatinine level > 133 μmol/L (1.5 mg/dL)
- Lack of improvement in serum creatinine level
    - i.e. lack of a decrease to a level of ≤ 133 μmol/L after ≥ 2 days following diuretic withdrawal and volume expansion with albumin
    - Recommended dose of albumin: 1 g/kg of body weight per day up to a maximum of 100 g/day
- Absence of shock
- Lack of current or recent treatment with nephrotoxic drugs
- Absence of parenchymal kidney disease as indicated by
    - Proteinuria >500 mg/day
    - Microhematuria (>50 RBCs/HPF)
    - And/or abnormal renal U/S

Clinical features

1- Type 1 HRS:

- Severe and rapidly progressive renal failure defined as doubling of serum creatinine, reaching > 2.5 mg/dL in < 2 weeks
- Usually severe liver failure (jaundice, encephalopathy, and coagulopathy).

- It may occur following a precipitating factor (severe bacterial infection, gastrointestinal hemorrhage, or therapeutic paracentesis without plasma expansion).
- It is the complication with the poorest prognosis in cirrhosis
- Median survival time is only 2 weeks

2- **Type 2 HRS**

- Moderate and stable renal failure
- Relatively preserved liver failure
- The main clinical consequence is refractory ascites
- Median survival is approximately 6 months

Treatment principles

1- **Liver transplantation:**

- Is the treatment of choice in patients with HRS

2- **Patients with HRS who undergo transplantation:**

- Have more complications, spend more days in the ICU and have a higher in-hospital mortality rate than patients without HRS who undergo liver transplantation

3- **Patients with HRS who are treated with vasopressin analogues and albumin before liver transplantation:**

- Have a post-transplant outcome similar to that of transplant recipients with normal renal function

4- **Patients with type 1 HRS:**

- Have an expected survival of < 2 weeks. So, liver transplantation become very unlikely unless survival ↑ by vasoconstrictors and albumin.

5- **Patients with type 2 HRS:**

- Usually have a sufficiently prolonged survival to allow liver transplantation.

6- **MELD score:**

- Has been implemented to assign organ allocation in patients on the waiting list for liver transplantation
- This score takes into account serum bilirubin level, INR and serum creatinine level
- These patients have a short survival, and to reach liver transplantation, they must have a high priority on the waiting list

Treatment of type 1 HRS

1- **Terlipressin:**
  - Type 1 HRS is reversible following treatment with terlipressin (VC analogue of ADH) and I.V. albumin
  - Mechanism: VC of splanchnic circulation
  - A delay of several days occurs between the improvement in circulatory function and the increase in GFR
  - Concurrent systemic VC may potentially cause ischemic side effects
  - Reversal of HRS improves survival, and a significant number of patients may undergo liver transplantation
  - Recurrence of HRS after treatment with terlipressin is not frequent, and readministration of the same treatment should be considered
  - Approximately 40% of patients with HRS respond to treatment with terlipressin and albumin

2- **Catecholamines** (midodrine and norepinephrine):
  - Also effective but more studies are needed

3- **TIPS:**
  - improves renal function in patients with HRS
  - Recommended for patients who cannot receive vasoconstrictor drugs and have no contraindications to TIPS

4- **Hemodialysis:**
  - Not effective in the treatment of HRS
  - Used only if patients have specific clinical indications (hypervolemia, tubular acidosis, hyperkalemia).

5- **Extracorporeal albumin dialysis:**

- improve renal function in patients with type 1 HRS
- However, one study showed that molecular adsorbent recirculating system (MARS) treatment is not associated with an increase in GFR

Treatment of type 2 HRS

1- Management is mainly focused on the treatment of **refractory ascites**

2- **No studies** evaluate the effect of vasoconstrictor treatment on renal function in patients with type 2 HRS

3- **Only two pilot studies:** specifically assessed TIPS in type 2 HRS and concluded that TIPS is effective in reversing type 2 HRS but more data on complication rate and survival are needed

Prevention of HRS

In four specific situations, HRS may be successfully prevented:

Condition	Intervention	Effect
Therapeutic paracentesis	Albumin (8 g/L of ascites removed) if > 5 L	↓ risk of HRS and hyponatremia
SBP	Albumin (1.5 g/kg IV at diagnosis of the infection and 1 g/kg after2 days)	↓ risk of HRS type 1 , Improves survival and ↓ impairment in circulatory function
Primary prophylaxis of SBP	Long-term oral norfloxacin (400 mg/day)	↓ the risk of type 1 HRS
Severe acute alcohol hepatitis	Pentoxifylline (400 mg t.i.d. p.o.)	↓ risk of HRS and Improves survival

1- **In SBP:**

- Give also I.V. cefotaxime 1 gm twice daily for 5-7 days

2- **In primary prophylaxis of SBP:**

- Using long-term oral norfloxacin in patients with low protein ascites (< 1.5 mg/dL) and serum bilirubin > 4 mg/dL associated with a Child–Pugh score > 9, or serum creatinine > 1.2 mg/dL, was associated with a significant decrease in 1-year probability of development of SBP (7% versus 61%) and type 1 HRS (28% versus 41%) and a significant increase in the 3-month and 1-year probability of survival (94% versus 62% and 60% versus 48%, respectively).

3- **Pentoxifylline:**

- ↓ Incidence of HRS (8% in the pentoxifylline group versus 35% in the placebo group) and the hospital mortality (24% versus 46%, respectively).

TUMORS OF THE LIVER

Hepatocellular carcinoma

Risk factors

Known	Possible
Cirrhosis (of any cause)	Alcohol (in absence of cirrhosis)
Chronic hepatitis B	Smoking
Chronic hepatitis C with cirrhosis	Anabolic or estrogenic steroids
Nonalcoholic steatohepatitis with cirrhosis	DM, obesity
Inherited metabolic disorders: - Alpha-1 antitrypsin deficiency - Hemochromatosis - Hereditary tyrosinemia	
Carcinogens: - Aflatoxin	

- Thorotrast	

1- **Chronic hepatitis B:**

- The most common etiologic agent in high incidence areas
- The mechanism is liver regeneration and injury characteristic of cirrhosis
- HBV is a DNA virus: its genome integrated within the genome of hepatocytes which influence actions of oncogens or tumor suppressor genes
- The protein of HBV is atransactivator (transform into DNA)

2- **Chronic hepatitis C:**

- The most common etiologic factor in areas of intermediate incidence
- HCV is RNA virus (not integrated)
- Almost all cases of HCV- related HCC associated with cirrhosis or advanced fibrosis
- Alcohol may be an important co-factor

Clinical features

1- **Gender :** males > females

2- **Age:** 4th decade in high incidence areas and old age in other areas

3- **Suspicion :**

- In any patient with liver cirrhosis and rapid unexplained deterioration, HCC should be suspected

4- **Abdominal pain or discomfort + weight loss:**

- Are the most frequent presenting symptoms

5- **Acute abdomen:** occasionally if rupture

6- **Asymptomatic:**

- In many patients the tumor detected incidentally or during screening of at-risk persons

7- **± Paraneoplastic manifestations:**

- Hypoglycemia: insulin like growth factor and ↑ demand by tumor mass
- Erythrocytosis: erythropiotin
- Hypercholesterolemia
- Feminization

8- **Refractory ascites**, liver cell failure and jaundice

9- **The liver:** enlarged, irregular, tender and hepatic bruit may be audible

Diagnosis

1- **U/S:** can detect Small HCCs (0.5 to 1 cm), as hypodense lesions

2- **CT:**

- Confirm tumors > 2 - 3 cm in diameter
- Detect the extent of tumor within the abdomen

3- **Multiphasic CT or MRI with multiphase images:**

- Has greatly enhanced the sensitivity of detection
- lesion has a characteristic appearance with arterial enhancement and venous washout

4- **Alpha fetoprotein (AFP):**

- Approximately 80% - 90% of patients have ↑ serum AFP (up to > 400-500ng/ml)
- Most patients with a small tumor (< 5 cm) have normal or minimally elevated levels
- AFP values may be raised in patients with chronic viral hepatitis and cirrhosis without HCC
- AFP is sensitive but not specific

5- **AFP-L3:**

- Represents a lectin-bound fraction of AFP that may be more specific than AFP for HCC

6- **Liver biopsy:**

- May be required to confirm a diagnosis of HCC
- Better avoided because of seeding of malignant cells

- The risk of bleeding after liver biopsy is slightly higher than after liver biopsy for benign disease
- Biopsy of the nontumorous portion of the liver is advisable to evaluate the severity of underlying liver disease, particularly if resection is contemplated

7- **Fibrolamellar HCC:**

- Is a variant of HCC usually not associated with cirrhosis or any of the other known etiologic factors with better prognosis

Treatment

1- **The overall outlook is poor**

- In Africa and Asia, where the diagnosis is often made when the tumor is at an advanced stage, HCC is associated with mean survival times measured in weeks to months

2- Scheme for the management of patients with HCC

Extent of tumor	Cirrhosis	Treatment options
Confined to liver	No	Large-scale resection
Confined to liver	Yes, compensated	Segmentectomy; consider Ethanol injection, RFA, Chemoembolization, or Liver transplantation
Confined to liver	Yes, decompensated	Liver transplantation
Spread beyond liver	Yes or no	Sorafenib

3- **Surgery:**

- If cirrhosis is not present → Large scale resections of the liver
- In a cirrhotic liver → small resections, segmentectomy, or enucleation, so most patients are not amenable to surgery at the time of diagnosis because of the extent of the tumor or severity of the underlying liver disease
- Rates of recurrence and development of new tumors after resection are high

4- **Liver transplantation:**

- Survival rate similar to that of resection in patients with cirrhosis, but with a lower recurrence rate
- HCC now represents an important indication for liver transplantation in developed Western countries

5- **Radiofrequency ablation (RFA):**
  - Percutaneous technique allows complete ablation of liver tumors with only one or two sessions
  - Indicated in small tumor with compensated cirrhosis

6- **Injection of absolute ethanol**
  - Causes tumor coagulative necrosis and thrombosis of tumor vessels
  - Easy to perform, with few side effects
  - Indicated in tumors < 4 cm, in patients with decompensated cirrhosis who will not tolerate surgery or in cases of recurrent HCC after surgery

7- **Chemoembolization:**
  - Chemotherapeutic agents are injected into the hepatic artery, which is subsequently occluded, is effective in shrinking tumors and improves survival in selected patients

8- **Targeted molecular therapies:**
  - Appear promising in the treatment of HCC
  - Sorafenib, a multikinase inhibitor, has been shown to improve survival in patients with advanced HCC

9- **Systemic chemotherapy:**
  - Not effective as regional chemotherapy (administered through the hepatic artery)
  - Cisplatin, in combination with other agents, appears to be the most effective agent.

Prevention [see chronic hepatitis]

1- HCC is potentially a preventable form of cancer

2- **HBV vaccination:**
  - ↓↓ The rate of HCC in many high-incidence areas of the world.

3- **The incidence of HCV infection:**

  - May also decline because of increased awareness and screening of donated blood

4- At present, an effective vaccine is not available against HCV

5- **Antiviral therapy:**

  - Eliminate HCV infection and decrease the risk of HCC

6- **Nucleos(t)ide analogues:**

  - For HBV infection decrease the risk of HBV-related HCC

Focal liver lesions

Causes

1- **Benign tumors**

- Hepatocellular:
  - Focal nodular hyperplasia
  - Hepatocellular adenoma
- Biliary:
  - Biliary cystadenoma
  - Biliary hamartoma (von Meyemburg complex)
- Cystic:
  - Simple cyst
  - Hydatid cyst
  - Pyogenic/amebic abscess

- Mesenchymal:
  - Cavernous hemangioma
  - Lipoma
  - Angiomyolipoma
  - Leiomyoma
  - Fibroma
  - Teratoma
  - Solitary fibrous tumor
  - Myelolipoma
  - Myxoma
- Other lesions:

  - Focal fatty infiltration
  - Inflammatory pseudotumor

2- **Primary malignant tumors**

- Hepatocellular:
  - Hepatocellular carcinoma
  - Hepato-cholangiocarcinoma
  - Hepatoblastoma
- Biliary:
  - Cholangiocarcinoma
  - Cystadenocarcinoma
- Mesenchymal:
  - Angiosarcoma
  - Epithelioid hemangioendothelioma
  - Fibrosarcoma
  - Leiomyosarcoma
  - Liposarcoma
  - Undifferentiated sarcoma
  - Carcinosarcoma
  - Rhabdomyosarcoma
- Other: Lymphoma

3- **Metastatic tumors**

- Adenocarcinomas:
  - Colon, lung, breast, stomach, pancreas, prostate, ovary, urinary tract tumors, thyroid tumors
- Squamous cell:
  - Lung, esophagus, larynx, perineal tumors
- Others:
  - Sarcomas, lymphomas, melanomas and neuroendocrine tumors

Hepatic adenoma

1- **Definition**: This is a benign proliferation of hepatocytes

2- **Incidence**: rare tumor that occurs largely in female patients (OCP).

3- **Etiology:**

- Use of oral contraceptive pills
- Genetic abnormalities, including hepatocyte nuclear factor (HNF)–1α inactivation and β-catenin activation

4- **Clinical picture:**

- Patients typically present with pain or discomfort in the right upper quadrant
- Occasionally found incidentally
- Adenomas may rupture, resulting in hemoperitoneum

5- **Gross:**

- Usually single, but may be multiple, rarely with more than five lesions
- The size is variable but typically > 5 cm in diameter at diagnosis and sometimes massive
- Hepatic adenomatosis is a rare condition characterized by large numbers of adenomas in the liver with a high rate of recurrence

6- **Histologic examination** : shows benign hepatocytes organized in cords but with no portal triads

7- **Diagnosis:**

- CT, U/S or MRI → confirm the diagnosis
- Technetium (99mTc) radioisotope scan may show a defect within the liver
- The diagnosis may be confirmed by liver biopsy

8- **Treatment**:

- Discontinuing the use of estrogens
- Surgical resection is usually advisable, to obtain tissue to confirm the diagnosis and because of the risk of rupture and malignancy
- Liver transplantation may be considered for adenoma found in association with type I glycogen storage disease or hepatic adenomatosis because of the high risk of malignant transformation

Hemangioma

1- **Incidence:** relatively common, identified in at least 7% of autopsies

2- **Histology:**

- They are composed of an endothelial lining on a thin fibrous stroma making up cavernous, blood-filled spaces

3- **Gross:**

- Usually small; if > 10 cm in diameter, they are referred to as giant or cavernous hemangiomas

4- **Clinical picture:**

- Usually asymptomatic but, if large enough, may cause some abdominal discomfort
- Occasionally, thrombosis within a giant hemangioma may result in consumption of platelets and thrombocytopenia, particularly in children (Kasabach–Merritt syndrome)

5- **Prognosis:** increase in size over time but have no potential to become malignant

6- **Treatment:**

- Usually do not require any specific therapy
- May be resected if they are associated with significant symptoms
- Percutaneous needle biopsy should be avoided because of the risk of bleeding

Tumor like lesions of hepatocytes

1- Focal nodular hyperplasia (FNH)

- **Definition:** represents an abnormal proliferation of hepatocytes around an abnormal hepatic artery. The artery is usually embedded in a characteristic central stellate scar
- **Clinically:** usually silent and is typically found incidentally, often at the time of abdominal surgery for another reason
- **Gross:** In comparison with adenoma, FNH tends to be smaller and carries little risk of rupture. Multiple lesions are found in approximately 20% of patients
- **Diagnosis:**
  - A hepatic arteriogram may suggest the diagnosis if a tumor can be found surrounding a large hepatic artery
  - The diagnosis may be difficult to make on needle biopsy
  - Excisional biopsy may be required for diagnosis

- **Treatment:** Excisional biopsy is usually curative

2- Nodular regenerative hyperplasia (NRH)

- **Incidence:** increases with age and is found most commonly in persons > 60 years old
- **Pathogenesis**: is unknown but often appears to be related to obliterative venopathy involving portal vein branches
- **Histology:** diffuse formation of nodules composed of hepatocytes throughout the liver. The pattern is similar to cirrhosis, except these nodules do not have a surrounding rim of fibrosis
- **Association:** often associated with identifiable systemic diseases such as autoimmune disorders, rheumatoid arthritis (including Felty's syndrome), and myeloproliferative disorders
- **Complication:** often presinusoidal portal hypertension Patients may present with splenomegaly and hypersplenism or bleeding esophageal varices
- **Treatment:**
  - No specific therapy is available
  - Patients may require beta blocker therapy, endoscopic therapy, or rarely, portal decompression to prevent rebleeding from varices. Generally, patients with NRH tolerate variceal bleeding better than those with cirrhosis, presumably because they have relatively well-preserved hepatic synthetic function

3- Adenomatous hyperplasia (macroregenerative nodule, dysplastic nodule)

- **Definition:** This term is used for regenerative nodules of hepatocytes > 1 cm in diameter found in association with cirrhosis or, rarely, submassive hepatic necrosis. Adenomatous hyperplasia represents a form of dysplastic nodule
- **Complications:** strongly associated with the development of HCC
- **Treatment:**

- No specific therapy is needed
- In patients with cirrhosis, the presence of adenomatous hyperplasia should signal the need for intensive surveillance for the development of HCC

4- **Partial nodular transformation:**

- This rare condition is characterized by the presence of nodules of hepatocytes located in the perihilar region and associated with portal hypertension

Benign hepatic tumors of cholangiocellular origin

1- **Bile duct adenoma:**

- This is typically a solitary subcapsular tumor composed of a proliferation of small, round, normal-appearing bile ducts with cuboidal epithelium.

2- **Biliary microhamartoma** (von Meyenburg's complex):

- This is part of the spectrum of adult polycystic disease but may also be found together with polycystic disease (adult or childhood type), congenital hepatic fibrosis, or Caroli's disease

3- **Biliary cystadenoma:**

- This multiloculated cyst is analogous to mucinous cystadenomas of the pancreas. It has significant potential for development of malignancy.

4- **Biliary papillomatosis:**

- This rare condition consists of multicentric biliary tract adenomatous polypoid tumors that sometimes develop into adenocarcinoma (analogous to familial adenomatous polyposis).

Benign hepatic tumors of mesenchymal origin

Tumor	Comment
Mesenchymal hamartoma	Childhood tumor with a mixture of elements (bile ducts, vessels, and mesenchyma)
Infantile hemangioendothelioma	Tumor of infancy; may be complicated by thrombocytopenia, high-output heart failure; may require resection or ablation

Lipoma	Collection of lipocytes; distinct from focal fatty change within hepatocytes
Lymphangiomatosis	Masses of prominent, dilated lymphatic channels
Angiomyolipoma	Distinct radiographic appearance
Leiomyoma	Extremely rare
Fibroma	Solid fibrous tumor of the liver
Inflammatory pseudotumor	Chronic inflammation and fibrosis; may cause pain and fever
Myxoma	Myxomatous connective tissue

Metastatic disease

1- The liver is a **common site** of metastasis

2- Metastases are by far the **most common form** of hepatic malignancy

3- The **most frequent sites** of origin for hepatic metastases are lung, breast, and gastrointestinal and genitourinary tracts

Cholangiocarcinoma

1- Incidence:

- Much less common than HCC
- ≈ 25% of hepatobiliary cancers
- Age: 50 – 70 yrs
- Male to female ratio: 1.3: 1

2- Risk factors

- Primary sclerosing cholangitis
- Chronic hepatitis C with cirrhosis
- Clonorchis sinensis infestation
- Intrahepatic lithiasis, cholelithiasis
- Congenital anomalies (e.g., Caroli's disease)
- Exposure to Thorotrast
- Benign cysts, von Meyenburg's complex
- Inflammatory bowel disease

3- Clinical features

- Types: two basic types: peripheral and central
- The peripheral type:
    - Rarely associated with primary sclerosing cholangitis
    - Often manifests with abdominal pain (vague, nonspecific and mild) and weight loss
    - Palpable gallbladder: only with distal bile duct cancers
- The central type:
    - Arises in major bile ducts and is often associated with chronic inflammation in bile ducts, as in primary sclerosing cholangitis
    - Klatskin's tumors arise in the bifurcation of the bile duct
    - Central-type CCC often manifests with obstructive jaundice
      © Jaundice present in > 90 % of patients
      © Pruritus

4- **Diagnosis**

- The diagnosis of peripheral-type tumors: can be made by needle biopsy
- Central tumors : may be more difficult to diagnose because they arise in the presence of primary sclerosing cholangitis, so the bile ducts are already anatomically abnormal
    - Cytologic and histologic examination of material obtained by endoscopic brushing and biopsy, as well as direct cholangioscopy, may confirm the diagnosis
    - ↑ serum CA 19–9 may also be useful in establishing the diagnosis
- CCC may be difficult to distinguish from other forms of adenocarcinoma, and the diagnosis may be confirmed only at laparotomy or autopsy
- Mixed HCC/CCC may be found in association with cirrhosis

5- **Treatment**

- Peripheral CCC is sometimes amenable to resection
- Central CCC may also be resected particularly when small, as with Klatskin's tumors

- With both types, however, the recurrence rate after resection is high, and survival is poor
- Liver transplantation is currently not a viable therapeutic alternative in most patients because of the high post-transplant recurrence rate

Other tumors of the liver

1- Epithelioid hemangioendothelioma

- **Definition:** This tumor of vascular endothelial origin has low-grade malignant behavior. It may arise in organs other than the liver, particularly the lung
- **Diagnosis:** Malignant cells in this tumor stain positively for factor VIII
- **Histology:** The tumor must be distinguished histologically from angiosarcoma and CCC
- **Complications:**
    - Approximately 1/3 of patients have metastases
    - Vascular invasion is a prominent feature
- **Treatment:**
    - This tumor is important to recognize because of its malignant behavior and because it is potentially curable with extensive resection or even liver transplantation

2- Primary hepatic lymphoma

- **Incidence:_**Although 2ry involvement of the liver by lymphoma is common, 1ry lymphoma may also arise in the liver
- **Risk factors:** These tumors are often of B-cell origin and occur usually in patients with HIV infection and acquired immunodeficiency syndrome
- **Treatment:** respond poorly to chemotherapy and are associated with a poor prognosis

3- Angiosarcoma

- **Definition:** This is a high-grade malignant tumor of blood vessels arising within the liver

- **Predisposing factors**: are exposure to vinyl chloride monomers and exposure to the intravenous contrast agent Thorotrast
- **Treatment:** The tumor grows rapidly, responds poorly to radiation or chemotherapy, and has a poor prognosis

Pediatric tumors of the liver

1- Some tumors of the liver occur specifically in children. Furthermore, they often occur at specific ages

2- **Hepatoblastoma**

- Is a malignant tumor of hepatocytes that occurs in children < 2 years of age
- It is not associated with cirrhosis
- All patients have elevated serum AFP levels
- Hepatoblastoma is considered potentially curable with a combination of surgery and chemotherapy

3- **Although HCC** is typically a disease of adults, it has been recorded in children as young as 4 years of age in association with HBV infection

PORTAL HTN & VARICEAL BLEEDING

Portal hypertension

Definition [An increase in portal venous pressure]

1- Normal portal pressure: 5 - 10 mm Hg

2- Portal hypertension: > 12 mm Hg

3- Normal portal blood flow: 1 - 1.5 L/minute

4- Increased resistance to portal blood flow leading to formation of portosystemic collateral vessels that divert portal blood flow to the systemic circulation, thus effectively bypassing the liver

> Persistent pressure elevation of **> 12** mmHg in the portal vein circulation, dilation of the portal vein to **> 13** mm or an increase in the portal pressure gradient of **> 7** mmHg (difference between the pressure of the portal vein and that of the inferior vena cava)

Clinical consequences

1- **Varices:** gastroesophageal, anorectal, retroperitoneal, stomal, other

2- Portal hypertensive **gastropathy**, enteropathy, and colopathy

3- Caput medusa

4- **Ascites** and hepatic hydrothorax

5- Congestive **splenomegaly**

6- Hepatic **encephalopathy**

Causes and classification

1- Prehepatic

- Portal vein thrombosis
- Cavernous transformation of the portal vein
- Splenic vein thrombosis
- Splanchnic arteriovenous fistula
- Idiopathic tropical splenomegaly

2- Intrahepatic (some overlap exists)

- Presinusoidal: affects portal venule
    - Schistosomiasis (most common cause of portal hypertension worldwide)
    - Congenital hepatic fibrosis
    - Sarcoidosis

  - Chronic viral hepatitis
  - Primary biliary cirrhosis (early)
  - Myeloproliferative diseases
  - Nodular regenerative hyperplasia
  - Hepatoportal sclerosis (idiopathic portal hypertension)
  - Malignant disease
  - Wilson disease
  - Hemochromatosis
  - Polycystic liver disease
  - Amyloidosis
  - Toxic agents: copper, arsenic, vinyl chloride, 6-mercaptopurine

- Sinusoidal: affects sinusoids
  - All causes of cirrhosis (see Table below)
  - Acute alcoholic hepatitis
  - Severe viral hepatitis
  - Acute fatty liver of pregnancy
  - Vitamin A intoxication
  - Systemic mastocytosis
  - Peliosis hepatis
  - Cytotoxic drugs

- Postsinusoidal: affects central vein
  - Sinusoidal obstruction syndrome
  - Alcoholic central hyaline sclerosis

3- Posthepatic

- Hepatic vein thrombosis
  - Budd–Chiari syndrome
  - Vascular invasion by tumor

- Inferior vena caval obstruction
  - Inferior vena cava web
  - Vascular invasion by tumor

- Cardiac disease
  - Constrictive pericarditis
  - Severe tricuspid regurgitation

Etiology and diagnostic workup of the common causes of cirrhosis

Etiology	Diagnostic evaluation

Infection	
- Hepatitis B	- HBsAg, anti-HBs, anti-HBc, HBV DNA
- Hepatitis C	- Anti-HCV, HCV RNA
- Hepatitis D	- Anti-HDV
Toxins	
- Alcohol	- History, AST/ALT ratio, liver biopsy
Cholestasis	
- Primary biliary cirrhosis	- AMA, IgM, liver biopsy
- Secondary biliary cirrhosis	- MRCP, ERCP, liver biopsy
- Primary sclerosing cholangitis	- MRCP, ERCP, liver biopsy
Autoimmune hepatitis	- ANA, IgG level SMA, LKMA, liver biopsy
Vascular	
- Cardiac cirrhosis	- Echocardiogram, liver biopsy
- Budd–Chiari syndrome	- CT, US, MRI/MRA,
- Sinusoidal obstruction syndrome	History of offending drug use, liver biopsy
Metabolic	
- Hemochromatosis	- Iron studies, HFE gene mutation, liver biopsy
- Wilson disease*	- Serum and urinary copper, ceruloplasmin, slit lamp eye examination, liver biopsy
- Alpha-1 antitrypsin deficiency	- Alpha-1 antitrypsin level, protease inhibitor type, liver biopsy
- NASH	- Liver biopsy
Cryptogenic	- Exclude NASH, drugs

* **Should be** considered only in individuals aged 3-40 years who have unexplained hepatic, neurologic, or psychiatric disease

N.B Hypoalbuminemia is commonly found owing to the liver's impaired synthetic function

Diagnosis of portal HTN

The golden standard for diagnosis of portal hypertension is measurement of hepatic venous pressure gradient (HVPG), which is an invasive method. Portal hypertension can be assessed by detection of portal hypertension-related varices either invasively (endoscopy) or non-invasively (U/S, CT, MRI)

Ultrasonography (U/S, Duplex- Doppler)

1- **Features** suggestive of hepatic cirrhosis with portal hypertension include the following:
    - Nodular liver surface - However, this finding is not specific for cirrhosis; it can also be observed with congenital hepatic fibrosis and nodular regenerative hyperplasia
    - Splenomegaly
    - Ascites
    - Portosystemic Collateral circulation
    - Reversal of flow direction in the portal vein (hepatofugal flow).
2- **Normal features of portal vein**
3- Some studies have demonstrated that a **portal vein diameter > 13 mm** and the absence of respiratory variations in the splenic and mesenteric veins are sensitive but nonspecific markers of portal hypertension
4- It also can detect **thrombosis** of portal or splenic vein

CT scanning

1- **Findings** suggestive of portal hypertension
    - Collaterals arising from the portal system
    - Dilatation of the inferior vena cava
    - Ascites and splenomegaly
    - Abnormal configuration of the liver
2- **Diagnosis of fundal varices** by multidetector row CT "MDCT" is at least as accurate as endoscopic ultrasonography
3- **It's especially helpful in distinguishing** submucosal from perigastric fundal varices and is considered a less invasive alternative to conventional angiographic portography in assessing portosystemic collaterals
4- **Although, CT is not a recommended** screening method for detecting large esophageal varices, but it may be a cost-effective method of screening for varices and preferred to endoscopy by patients
5- **Limitations**
    - It cannot demonstrate the venous and arterial flow profile

- Intravenous contrast agents cannot be used in patients with renal failure or contrast allergy

MRI angiography

1- Detects the presence of portosystemic **collaterals**

2- It provides excellent detail of the **vascular structures of the liver** and can detect **portal venous thrombosis** and **spleen stiffness**

3- Provides quantitative data on portal venous and azygos **blood flow** which is increased in portal HTN

Upper GIT endoscopy

1- Screen for varices in every patient with suggestive findings of portal hypertension

2- **Risk factors warrants a screening** endoscopy for varices

- INR ≥ 1.5
- HVPG measurement ≥ 10 mm Hg
- Portal vein diameter > 13 mm
- Thrombocytopenia

3- **Indicators of ↑ risk of rebleeding**

- Variceal red color signs (eg, cherry red spots, red wale markings [longitudinal red streaks on varices], blue varices)
- "White nipple sign" (platelet fibrin plug overlying a varix, resembling a white nipple)

4- **Value**

- Direct visual evaluation of the size, location, and bleeding stigmata of the lesion
- Prompt therapeutic intervention
- Endoscopic staging of varices:
  - Grade I: small (< $^1/_3$ of esophageal lumen & < 5 mm in diameter), straight varices
  - Grade II: tortuous and occupying < $^1/_3$ of the esophageal lumen

- Grade III: large (> 5 mm in diameter), occupying > $^1/_3$ of the esophageal lumen

5- Gastroesophageal varices confirm the diagnosis of portal hypertension; however, their absence does not rule it out.

6- **Guidelines for periodic surveillance** endoscopy in cirrhotic patients

- In decompensated patients, patients with alcohol abuse, and patients with stigmata of variceal bleeding, repeat endoscopy annually
- In compensated patients with small varices, repeat endoscopy at 1-2 years to evaluate the progression of the varices
- In compensated patients without varices, repeat endoscopy at 2-3 years to evaluate for the development of varices

Endoscopic U/S

1- It's useful in measurement of transmural variceal pressure to allow estimation of variceal wall tension, which is a predictor of variceal bleeding

Hemodynamic measurement of portal pressure

1- In most cases, the diagnosis of portal hypertension can be based on physical findings; however, in some instances actual measurement of the portal pressure is required

2- **Patency of the portal vein** should be assessed before measurement by duplex Doppler ultrasound or MRA.

3- **Direct measurement of portal pressure** is invasive, expensive, complicated, and accurate

- Operative portal vein measurement (laparotomy)
- Percutaneous transhepatic measurement
- Transjugular measurement

4- **Indirect measurement of portal pressure** is the preferred method and is less invasive, safer, and less complicated

- Hepatic vein catheterization
  - Involves cannulation of the hepatic vein, balloon occlusion of the hepatic vein, and measurement of the wedged hepatic vein pressure (WHVP)
  - Can measure hepatic blood flow

- Intrasplenic measurement
  - Involves percutaneous puncture of the spleen
  - Not routinely performed

5- Predictive value

- Measurement of **HVPG** is a method for estimating PVPG.
- **HVPG** is the difference between the wedged or occluded hepatic venous pressure and the free hepatic venous pressure.
- **Portal venous pressure gradient**: defined as the difference between the portal pressure and that in the inferior vena cava
- **WHVP** actually a measure of sinusoidal pressure, not portal pressure
- HVPG has a **high correlation** with PVPG in patients with cirrhosis when hepatic resistance is sinusoidal or postsinusoidal, as in patients with alcoholic cirrhosis.
- HVPG tends to **underestimate** PVPG when the defect is presinusoidal, as in primary biliary cirrhosis & not useful also in detection of PVT where HVPG is normal
- An **HVPG of $\geq$ 10 mm Hg** is necessary for esophageal varices to form and bleed
- **According to Laplace's law**, variceal wall tension (*T*) is a function of the transmural pressure (TP) times the radius (*r*) of the varix divided by the variceal wall thickness (*w*): $T = (TP1 - TP2) \times r / w$
- **This calculation** combines measurements of variceal size and pressure and has the highest predictive value for determining the risk of EVH
- **Serial measurements of HVPG** are predictive of the risk of recurrent EVH.

* Patients who have a decrease in HVPG to a level $<$ 12 mm Hg either spontaneously or in response to pharmacologic therapy are not at risk for recurrent EVH and other complications of portal hypertension.

* Patients in whom HVPG decreases by $\geq$ 20% over the first few months after the index hemorrhage, usually in response to pharmacologic therapy, have a marked decrease in the risk of recurrent EVH

* Patients who have $<$ 20% decrease in HVPG while receiving pharmacologic therapy maintain a high risk of recurrent EVH

- **HVPG is also prognostic for survival**:

* The higher the HVPG, the worse the survival.

* HVPG also predicts the development of hepatic decompensation

* And also, the development of hepatocellular carcinoma

Transient elastography

1- Although measurement of HVPG and upper endoscopy are considered the criterion standards for assessment of portal hypertension, ultrasonography-based transient elastography is a **novel noninvasive** technology to detect clinically significant portal hypertension.

2- **The velocity of propagation** of the wave is directly related to the tissue stiffness, which correlates with fibrosis in liver disease

3- **In some studies**, liver stiffness showed an excellent correlation with fibrosis and HVPG in patients with recurrent HCV infection after OLT, it showed a sensitivity and specificity of 90% and 81% for the diagnosis of portal hypertension (HVPG $\geq$ 6 mm Hg).

4- **Further studies** are being conducted to validate this

Indirect indices of varices

1- **Platelet count, spleen size, albumin, and Child-Pugh score**, have been studied to help diagnose varices without endoscopy.

2- A case review study, however, revealed that some of these predictors are **unreliable**.

3- There is a study that showed that **platelet count/spleen diameter ratio** above 909 has a 100% negative predictive value for the presence of oesophageal varices

4- **Endoscopy** remains the criterion standard for screening patients with cirrhosis for varices

Management of portal HTN

1- Prevention of 1st variceal bleeding

2- Treatment of acute variceal bleeding

3- Prevention of recurrent variveal bleeding

4- Treatment of nonesophageal variceal sources of bleeding

5- Treatment of other complications: as HE and ascites

6- Treatment of the cause

Acute variceal bleeding

Risk factors for first variceal hemorrhage:

1- **Large** esophageal varices

2- Endoscopic red color signs

- Red weals, cherry-red spots and hematocystic spots
- These are essentially small varices on the surface of large varices

3- **Hepatic decompensation:**

- As evaluated by the Child–Turcotte–Pugh classification or the MELD score (ascites is a particular risk factor)

4- Active **alcohol** consumption in patients with alcoholic liver disease

Initial management

1- Resuscitation of the patient: [critical in the management]

- Adequate venous access → for blood and fluid replacement
- NGT or Ewald tube → to assess the severity of bleeding and to lavage gastric contents before endoscopy
- Fresh frozen plasma → if clotting factor deficiencies present
- Blood transfusions
    - To establish hemodynamic stability.
    - Caution should be taken not to overtransfuse the patient. In general, patients should be kept slightly undertransfused, usually with a hematocrit value of approximately 24, to avoid increasing portal pressure and exacerbating variceal bleeding
- Airway protection → in massive bleeding or HE
- Initiate antibiotic treatment
    - To reduce the risk of infection (cefotaxime 2 g I.V. /8hrs)

    - Before treatment, blood cultures, diagnostic paracentesis if ascites is present, and other studies as indicated should be performed
- Vit. K injection
- Initiate pharmacologic therapy → with vasoactive drugs (e.g., octreotide or terlipressin) as soon as possible and before endoscopy

2- **Endoscopy**

- The only reliable means for establishing the source of bleeding and should be performed as soon as the patient is adequately resuscitated
- Diagnostic findings in variceal hemorrhage
    - Direct visualization of bleeding **or**
    - More often, by endoscopic stigmata in patients with varices and no other visible source of bleeding (Endoscopic red color signs)

Endoscopic treatment

1- **EVL:**

- The endoscopic treatment of choice in the treatment of acute esophageal variceal hemorrhage (by elastic rings).
- Success rates of 80% - 90% in initial control of variceal hemorrhage
- Has few local complications, primarily mucosal ulceration

2- **Use of pharmacologic therapy** in conjunction with endoscopic therapy:

- improves the efficacy of endoscopic treatment in controlling acute bleeding
- Less re bleeding in the first 5 days and lower transfusion requirements

Pharmacologic treatment

1- **Advantages of vasoactive drugs:**

- Treatment can be started in the emergency room or even en route to the hospital, when variceal bleeding is suspected
- Unlike endoscopic therapy in which the effects of treatment are local, vasoactive agents lower portal pressure
- The use of vasoactive agents before endoscopy may offer the endoscopist a clearer view of the varices because bleeding is less active.

- Vasoactive agents can be useful for the treatment of sources of portal hypertensive bleeding other than esophageal varices, such as gastric varices more than 2 cm below the gastroesophageal junction or portal hypertensive gastropathy

2- **Available drugs:** [Treatment should be continued for 5 days]

Drug	Route	Administration	Dose
Terlipressin	IV	Initial bolus Subsequent bolus	2 mg/4 hr 1–2 mg/4 hr
Somatostatin	IV	Initial bolus Continuous infusion	250–500 µg 250–500 µg/hr
Octreotide	IV	Initial bolus Continuous infusion	25–50 µg 25–50 µg/hr

3- Although in common usage throughout the world, none of these agents is approved by the FDA for this indication

4- **The combination of vasopressin and nitroglycerin (Pitressin):**

- Controls variceal bleeding in a higher percentage of patients than vasopressin alone
- The addition of nitroglycerin ameliorates many of the systemic side effects of vasopressin and thus renders vasopressin more tolerable
- Dose of vasopressin is 20iu/hr I.V. drip
- Action: vasospasm in splanchnic arterioles → ↓ blood flow to intestine → decrease of portal HTN
- Side effects: generalized vasospasm e.g. MI (add nitrates)

5- **Somatostatin:**

- Effective in controlling variceal bleeding in 60% - 80% of patients with no serious side effects

6- **Octreotide:**

- Synthetic analogue of somatostatin with a longer half-life
- A metaanalysis concluded that octreotide was superior to vasopressin/terlipressin in controlling acute variceal bleeding

7- **Vapreotide and lanreotide:**

- Are somatostatin analogues that are currently under investigation

8- **Terlipressin (Glypressin):**
  - Synthetic analogue of vasopressin with longer half-life than vasopressin and therefore can be given by I.V. bolus infusion
  - Randomized controlled trials concluded that the drug is more effective than vasopressin, with far fewer side effects. It is used widely in Europe, and approval by the FDA is pending
  - Action: decreases portal pressure without systemic effects (selective)

Balloon tamponade [replaced now by endoscopy]

1- **Indications**
  - Temporizing treatment for failures of pharmacologic and endoscopic therapy, before more definitive treatment for the control of acute variceal bleeding is undertaken

2- **Success with balloon tamponade**
  - Can often be achieved with inflation of just the gastric balloon, thereby avoiding the additional complications associated with use of the esophageal balloon

3- **Complication rates:**
  - With the use of balloon tamponade relate to the experience of the team using the balloon

4- **Specific precautions:**
  - Required to minimize the risk of aspiration and asphyxiation.
  - The balloon should not be kept inflated for more than 24 hours because of the risk of esophageal necrosis.
  - Tube should be removed in endoscopy room

TIPS

1- **Indicated in:** high-risk patients
  - Child's class C
  - Child's class B with active bleeding at endoscopy

2- The placement of TIPS using a coated stent within 24 hours of admission may result in **less morbidity and improved survival** compared to standard medical therapy

Treatment for failures of medical therapy

1- A National Institutes of Health consensus conference supported the use of **TIPS:** for the rescue of the 10% - 20% of patients in whom medical therapy fails to control acute variceal hemorrhage

2- In experienced hands: **TIPS can be successful in 90% - 95%** of patients, with relatively low immediate mortality compared with the use of surgical shunts

3- Rebleeding and hepatic encephalopathy are long-term complications of TIPS, but are less of a risk with the advent of coated stents

4- In a few selected centers: the early (within 12 hours of diagnosis) use of **portosystemic shunt surgery** has been advocated, with excellent results reported. However, this approach has not gained widespread acceptance

Prevention of recurrent variceal hemorrhage

1- Concepts

- **The risk for recurrent variceal bleeding** is highest in the first few weeks, and the risk of rebleeding remains significantly elevated during the first 6 months after the index hemorrhage
- Therapy to prevent recurrent bleeding should be **initiated as soon as** the acute bleeding episode is adequately controlled

2- Endoscopic therapy

- **EVL:**

  - Has replaced sclerotherapy as the endoscopic therapy of choice for the prevention of recurrent variceal bleeding.
  - When compared with sclerotherapy, EVL is associated with lower rates of recurrent bleeding, mortality, and complications and requires fewer sessions for variceal obliteration

- **The combination of EVL and sclerotherapy:** offers no advantage over EVL alone
- **Regimen of EVL:**
  - At regular intervals (every other week) until the varices are obliterated
  - Followed by regular surveillance with repeat endoscopic treatment if varices recur

3- Pharmacologic therapy

Drug	Initial dose	Therapeutic dose (range/day)
Propranolol	40 mg b.i.d.	40–400 mg
Nadolol	40 mg q.d.	40–160 mg
Timolol	10 mg q.d.	5 mg q.d.–40 mg
Isosorbide 5-mononitrate	20 mg b.i.d.	20 mg t.i.d.–20 mg q.i.d.

- **Effect** of nonselective beta-adrenergic blockers (propranolol, nadolol):
  - Reduce the risk of recurrent variceal bleeding and mortality associated with bleeding.
- **Indications** of beta blocker therapy:
  - Patients with good hepatic function (Child's classes A and B)
  - Patients deemed to be compliant with taking medication
  - If no contraindications to use of beta blockers (e.g., congestive heart failure, severe chronic lung disease)
- **Action of beta blockers:**
  - ↓ portal pressure by splanchnic VC and to a lesser extent by decreasing cardiac output

  - May make resuscitation more difficult if the patient bleeds
- **The therapeutic dose of beta blockers:**
  - Is adjusted to the highest tolerated dose (dose that ↓ HR by 25%)
- In centers where **hepatic hemodynamic measurements** available:
  - Serial measurements (baseline and at 1 to 3 months) of the HVPG are predictive of the efficacy of treatment
  - Recurrent variceal bleeding is significantly reduced when
    HVPG decreases to < 12 mm Hg
    At least a 20% decrease in HVPG from baseline is noted
- If therapy with beta blockers does **not achieve** one of these end points:
  - Add a second drug (e.g., a long-acting nitrate) to reduce HVPG further.
- **Carvedilol:**
  - Nonselective beta blocker with intrinsic anti–alpha-1-adrenergic activity
  - Decrease portal pressure to a greater extent than selective beta blockers and is reasonably well tolerated
  - Studies are needed to determine the clinical role of this agent

4- Combined endoscopic and pharmacologic

- The preferred option for the prevention of recurrent variceal bleeding

5- Treatment for failures of medical therapy

- **TIPS**
  - Effective at reducing portal pressure
  - The preferred treatment for patients in whom initial medical therapy fails, especially for those with poor operative risks
- **Portosystemic shunt surgery:** (remains an alternative)
  - Indicated for low-risk patients (Child's class A)
- **Distal splenorenal shunt:**

- Preferable to portosystemic shunt in patients with nonalcoholic cirrhosis because of the lower frequency of hepatic encephalopathy associated with the selective shunt

- **Liver transplantation:**
  - Considered for patients with end-stage liver disease
  - Selection of candidates depends on the patient's clinical status, the cause of cirrhosis, abstinence from alcohol in patients with alcoholic cirrhosis, and the availability of a donor organ
  - For patients who are candidates for liver transplantation, a TIPS procedure can be used as a bridge to transplantation

Management of nonesophageal variceal sources of bleeding

Gastric varices

1- Gastric varices that extend **more than 5 cm** below the gastroesophageal junction or are isolated to the fundus are at high risk for bleeding

2- Endoscopic treatment for gastric varices is less effective than for esophageal varices. Although **band ligation and injection with cyanoacrylate glue** have been somewhat effective in the management of bleeding gastric varices

3- **Pharmacologic therapy** should be considered for initial treatment of acute bleeding and prevention of recurrent bleeding

4- Patients who fail pharmacologic therapy should be considered for **TIPS**, shunt surgery, or liver transplantation

Portal hypertensive gastropathy

1- Portal hypertensive gastropathy is a common complication of cirrhosis and portal hypertension, but significant gastrointestinal bleeding from this source is relatively uncommon

2- **It ranges from** a mild form characterized by a diffuse mosaic mucosal pattern to more severe forms characterized by brown spots, cherry red spots, a granular mucosa, and diffuse mucosal hemorrhages

3- **Treatment of esophageal varices** with sclerotherapy has been associated with an increase in the severity of portal hypertensive gastropathy

4- **Pharmacologic therapy is the only** medical option for treating acute bleeding or preventing recurrent bleeding from portal hypertensive gastropathy. Endoscopic therapy has no role

5- For the uncommon failures of medical therapy, **TIPS**, surgical shunts, or liver transplantation are the options for rescue

METABOLIC & INHERITED LIVER DISEASES

Hemochromatosis

Definition

1- Hereditary hemochromatosis (HH) is an **inherited disorder** characterized by **iron-mediated tissue injury** (excessive iron deposition in various organs) secondary to impaired regulation of intestinal iron absorption

Genetics

1- HH is associated with **mutations in genes encoding proteins**, with the common feature of iron overload resulting from unregulated intestinal iron absorption

2- **Type 1 HH,** or *HFE*-associated HH, is the most common form of HH and is inherited as an autosomal recessive trait (chromosome 6).

3- Although the *HFE* gene mutation is highly prevalent in the white population, **its penetrance is quite low**; therefore, relatively few patients homozygous for the C282Y mutation in the *HFE* gene manifest the complete phenotype

Classification

1- **Type 1 (HFE- hemochromatosis)**
   - Factors influence iron absorption and accumulation may explain the clinical variability in phenotype:
     - Vitamin C (ascorbic acid) intake
     - Amount of iron in diet
     - Bioavailability of dietary iron
     - Type of dietary iron (heme iron absorption > nonheme)

2- **Type 2 HH:**
   - More severe iron overload and resultant tissue damage earlier in life than in patients with HFE HH

3- **Type 3 HH:**
   - Manifestations similar to those of HFE HH

4- **Type 4 HH:** has distinct clinical and histologic manifestations:
   - Transferrin-iron saturation may be normal with elevated ferritin
   - Iron is deposited predominantly in RES cells in the liver
   - Patients may tolerate phlebotomy poorly
   - All forms of HH are inherited as autosomal recessive traits, except for type 4 HH, which is inherited as an autosomal dominant trait

Mutations associated with HH

Type	Common name	Associated gene and gene product
Type 1	Classic hemochromatosis	*HFE* (HFE)
Type 2A	Juvenile hemochromatosis	*HFE2* (haemojuvelin)
Type 2B	Juvenile hemochromatosis	*HAMP* (hepcidin)
Type 3	*Tfr2*-related hemochromatosis	*Tfr2* (transferrin receptor-2)
Type 4	Ferroportin-related iron overload	*SLC40A1* (ferroportin)

Clinical features

1- **Gender:** Males > females

2- **Age:** Around 40 yrs

3- **Course:** slowly progressive

4- **Before 1960**, HH were often diagnosed on presentation with classic features of
  - Bronze DM
  - Arthritis
  - Liver disease
  - Heart failure

5- **Now:** diagnosis most commonly made in the asymptomatic phase through laboratory testing

6- **The diagnosis of asymptomatic HH** is often made following discovery of elevated serum iron markers in the following clinical situations:
  - Elevated serum aminotransferase levels
  - Evaluation of serum iron markers
  - Family or population screening

7- **When diagnosis made after onset of symptoms**, the most common symptoms at the time of diagnosis are as follows:
  - Weakness, lassitude, lethargy, or fatigue
  - Arthralgias or arthritis (women more commonly than men)
  - Nonspecific right upper quadrant pain
  - Loss of libido or potency (men)

8- **Other manifestations** include the following:
  - Increased skin pigmentation: bronzed color or leaden grey skin pigmentation in axillae, groins, genitalia and exposed areas due to excessive melanin deposition
  - Diabetes mellitus
  - Amenorrhea
  - Liver involvement
  - Cardiac involvement
  - Infections

Liver disease

1- Increased hepatic iron concentration: is present in patients with HFE HH and elevated serum ferritin
2- The **severity of liver disease**: generally correlates with the severity of hepatic iron overload, although coexisting liver diseases can add to the degree of liver injury
3- Elevation of serum **aminotransferase**: mild, and frequently normalize once excess iron stores are removed.
4- If iron depletion is achieved and maintained **before hepatic fibrosis** or cirrhosis: the risk of further liver complications is not increased
5- Once cirrhosis developed: patients remain at increased risk of **HCC** even after iron depletion
6- **Increased prevalence rates** of chronic viral hepatitis B and C and heavy alcohol intake: have been reported in patients with phenotypic HH.
7- **Heavy alcohol intake:** associated with increased morbidity in patients with HH

Cardiac disease

1- **HH (especially type 2):** can be associated with cardiac dysfunction and arrhythmias
    - Restrictive cardiomyopathy or dilated cardiomyopathy
    - Atrial and ventricular dysrhythmias
2- Cardiac involvement occurs **relatively late** in the course of HFE HH: and iron depletion before the development of dilated cardiomyopathy improves cardiac function. Thus, cardiac dysfunction is now seen less commonly because most patients are diagnosed and treated before cardiac involvement occurs
3- **Cardiomyopathy:** is a major cause of postoperative morbidity and mortality after liver transplantation

Diabetes mellitus

1- Probably results from iron deposition in the pancreas
2- It may be associated with increased plasma insulin levels, a finding suggesting peripheral insulin resistance (type 2) particularly with associated liver disease

Joint disease

1- Major cause of morbidity
2- It **characteristically involves**: the 2nd and 3rd metacarpophalangeal joints; other metacarpophalangeal joints and wrist joints are also frequently involved; joints less commonly affected include shoulder, hip, knee, and ankle
3- **Pathologic features** include: joint space narrowing, chondrocalcinosis, subchondral cyst formation, and osteopenia
4- It does **not improve** with iron depletion

Infections

1- Patients with HH have **increased risk** of bacterial, viral, and fungal infections.
2- Increased risk of infections **result from** iron-mediated impairment of innate and acquired immune responses
3- **Unusual bacterial infections** associated with HH:
    - Vibrio vulnificus
    - Yersinia enterocolitica
    - Yersinia pseudotuberculosis
    - Listeria monocytogenes

Natural history and prognosis

1- **Liver disease is slowly progressive** but is usually mild (except with hepatitis or alcohol abuse) when the hepatic iron concentration < 200 μmol/g dry weight of liver
2- **Liver failure or HCC** accounts for 60% of iron overload–related mortality
3- Patients with HH and cirrhosis have a significantly increased risk of **HCC** (20- to 200-fold increased risk).
4- **Cholangiocarcinoma** may occasionally develop
5- Concern exists about an increased risk of **nonhepatobiliary cancers** in HH, but the data are conflicting
6- **Some manifestations improve** with iron depletion (malaise, fatigue, skin pigmentation, diabetes mellitus, abdominal pain), whereas others do not (arthropathy, hypogonadism, cirrhosis).

7- **Patients without cirrhosis or diabetes mellitus** have a normal life expectancy if they adhere to treatment

8- **Patients with cirrhosis or diabetes mellitus** have a significantly decreased life expectancy, but the prognosis is improved with iron depletion therapy

9- Patients with HH may need **liver transplantation** for end-stage liver disease or HCC

10- Liver transplantation in patients with HH is associated with an increased risk of **infections,** especially fungal infections, and decreased survival

11- HH is reportedly associated with even **worse post-transplant outcomes** than other causes of iron overload

Diagnosis

1- Clinical suspicion and laboratory tests

- HH should be considered in these situations
    - Degenerative arthropathy
    - Unexplained hepatomegaly or liver disease
    - Unexplained hypogonadism (pituitary dysfunction)
    - Elevated serum transferrin saturation or ferritin
- Serum transferrin–saturation and ferritin are the first tests to be obtained when considering HH
- Serum transferrin–saturation is more sensitive and specific than ferritin:
    - Serum transferrin–iron saturation is the earliest manifestation of HH
    - Serum ferritin is an acute phase reactant and can be elevated in inflammatory conditions and other chronic liver diseases (e.g., nonalcoholic steatohepatitis, chronic hepatitis C and alcoholic liver disease).
- Circadian and postprandial variations of transferrin saturation: can be a source of laboratory error, so the test is best done after overnight fasting
- Transferrin saturation > 45% warrants further evaluation for HH

- Isolated elevation of ferritin with normal transferrin–iron saturation: may indicate type 4 HH
- High serum iron and low IBC

2- Genotyping

- HFE mutation analysis: should be done in all individuals with persistently elevated transferrin-iron saturation, especially if serum ferritin is also elevated
- The presence of C282Y homozygosity or C282Y/H63D compound heterozygosity: confirms the diagnosis of HFE HH in the appropriate clinical setting
- Genetic tests for non-HFE HH: are not currently available for clinical use

3- Liver biopsy

- Indicated in 2 clinical situations:
  - For diagnosis when *HFE* genotyping is negative in suspected HH
  - For staging (presence or absence of cirrhosis) in confirmed HFE HH

- Liver biopsy for diagnosis involves two studies:

Study	Comments
Hepatic iron index (hepatic iron concentration in µmol/g dry weight divided by the patient's age in years) measured in fresh or preserved tissue	≥1.9 is frequently observed in patients with phenotypic HH, but in many C282Y homozygotes the index is <1.9.
Staining for hepatic iron (Perls' Prussian blue stain)	important because sampling variability can yield a low hepatic iron index

- Liver biopsy for staging is important because of the following:

- Histopathologic study is the only reliable method for determining the presence or absence of cirrhosis in the absence of clinical signs
- The presence of cirrhosis is associated with an increased risk of mortality and HCC
- Knowledge of the presence or absence of cirrhosis may influence management (e.g., patients with cirrhosis need surveillance for HCC).

- Staging with liver biopsy is required only in C282Y homozygotes with elevated serum aminotransferase levels or serum ferritin levels > 1000 µg/L: because the likelihood of cirrhosis is low in the absence of these two findings

4- **Other tests**

- Hepatic MRI:
  - can quantitatively estimate hepatic iron; it is devoid of the two principal disadvantages of liver biopsy: invasiveness, and sampling variability
- Quantitative phlebotomy:
  - useful for estimation of iron overload when liver biopsy is not required
  - Each phlebotomy usually removes 500 mL of blood (approximately 250 mg of iron); a need for removal of ≥ 4 g of iron before the onset of iron-limited erythropoiesis indicates the presence of significant iron overload

Differential diagnosis

1- **Secondary iron overload** can occur in the following situations:

- Increased RBCs turnover (e.g., disorders of ineffective erythropoiesis)
- Repeated blood transfusions
- Combination of the previous factors

2-**Major causes of secondary iron overload** (Hemosiderosis):

- Iron-loading anemias with or without transfusion
    - Thalassemia major
    - Sideroblastic anemia
    - Chronic hemolytic anemias
- Dietary iron overload (rare)
- Iron overload associated with chronic liver diseases
    - Alcoholic liver disease
    - Chronic hepatitis B and C
    - Nonalcoholic fatty liver disease
- Miscellaneous causes
    - Porphyria cutanea tarda
    - African iron overload
    - Neonatal hemochromatosis
    - Aceruloplasminemia
    - Atransferrinemia

3-**The following features differentiating** 2ry iron overload associated with chronic anemias from HH:

- Liver biopsy in secondary iron overload shows iron overload primarily in Kupffer cells and RES cells, with a paucity of iron in hepatocytes (not in parenchyma = minimal damage). A periportal to pericentral "iron gradient" is also not observed in these conditions; however, a similar pattern may be observed in type 4 HH
- Quantitative phlebotomy: demonstrates the onset of iron-limited erythropoiesis before removal of 4 g or more of iron
- MRI: show that the pancreas is spared in 2ry iron overload (hemosiderosis)

Treatment

1- **Iron depletion by serial phlebotomy:** is the cornerstone of therapy of HH

2- **Suggested protocol for serial phlebotomy:**

- Phlebotomy is performed, with removal of 500 mL of blood (approximately 250 mg of iron) weekly or biweekly until serum ferritin is 50 - 100 µg/L

- The hematocrit should be checked before each session, and serum ferritin should be assessed every 3 months (after every 10 - 12 phlebotomies).
- If the hematocrit is < 32%, phlebotomy should be postponed, and the frequency should be decreased to once in 2 weeks
- Once serum ferritin is < 50 μg/L, it should be checked every 3 to 4 months, and phlebotomy should be repeated as required to keep serum ferritin at 50 - 100 μg/L
- The required frequency of maintenance phlebotomy depends on the rate of iron accumulation (generally required once in 2 - 4 months).

3- **Precautions during phlebotomy:**

- Anemia prevented by monitoring hematocrit before each phlebotomy and ensuring adequate dietary protein, vitamin B12, and folate intake
- High doses of ascorbic and citric acid, as well as a diet rich in iron, should be avoided. Moderate consumption of red meat is permissible
- Alcohol should be avoided while iron depletion therapy is in progress

4- Because of **increased susceptibility to *V. vulnificus* infection**: patients should avoid eating uncooked seafood and exposing open wounds to warm coastal seawater. Susceptibility to *V. vulnificus* infection does not resolve with iron depletion therapy

5- **Iron chelators** (deferoxamine, deferiprone, and deferasirox) are less effective, are more expensive with adverse effects. Thus, these drugs are used only in patients with anemia or those who cannot tolerate phlebotomy as heart failure.

6- **Symptomatic treatment:**

- D.M. → insulin
- Hypogonadism → androgens (testosterone proprionate IM)
- Cardiomyopathy →

Screening

1- **Family screening**

- All first-degree relatives of confirmed HH should undergo screening

- HFE mutation analysis or fasting transferrin-iron saturation and ferritin is suggested for screening
- Relatives of patients with HFE HH who are negative for *HFE* mutations do not require any further testing
- Relatives who are positive for *HFE* mutations should be monitored with annual ferritin levels, and phlebotomy should be initiated when appropriate

2- Population screening

- Controversial.
- Genotypic screening (*HFE* mutation analysis): is not recommended, given the low penetrance of HH and concerns of psychological harm and genetic discrimination
- Phenotypic screening (transferrin-iron saturation) : is suitable for population screening, but negative results in young adults should be interpreted with caution because those individuals may subsequently develop elevated transferrin-iron saturation

Wilson's disease

Pathophysiology

1- Normally:

- Dietary copper is absorbed from the stomach & proximal small intestine and is rapidly taken into liver where it's stored and incorporated into ceruloplasmin which is excreted into blood
- Accumulation of excessive copper in the body is prevented by excretion:
  - Mainly bound to ATPase Wilson disease protein (WDP) and excreted into bile
  - A small fraction of serum albumin-bound "nonceruloplasmin" copper is excreted by kidney

2- In Wilson's disease:

- **Mutations in ATP7B** gene on chromosome 13 that codes for Wilson disease protein (WDA), resulting in retention of copper in the liver and impaired incorporation of copper into ceruloplasmin
- Biliary excretion of copper is reduced in Wilson's disease
- Deficiency of the plasma copper protein ceruloplasmin is **unlikely** to have a role in the pathogenesis of Wilson's disease. It is believed that the low serum ceruloplasmin level in Wilson's disease patients is the result of a lack of incorporation of copper into apoceruloplasmin, which has a shorter half-life than copper-bound ceruloplasmin
- **Excess copper in liver** appears to exhibit toxicity by the generation of free radicals, which result in lipid peroxidation, depletion of antioxidants, and polymerization of Cu-thionein leading to necrosis and apoptosis
- Pathologic copper deposition in the **basal ganglia of the brain**, particularly in the caudate nucleus and the putamen, results in the neurologic and psychiatric manifestations of the disease, while excessive deposition in Descemet's membrane of the cornea gives rise to Kayser–Fleischer rings

Clinical features

- ■ Clinical symptoms are rarely observed before age 5 years, and most untreated patients become symptomatic by the age of 40 years

- In one large series the initial clinical manifestations were **hepatic** in 42%, **neurologic** in 34%, **psychiatric** in 10%, and **hematologic in** 12%.
- Other less common manifestations include renal, skeletal, cardiac or dermatologic symptoms

1- **Hepatic:** tend to occur at a younger age (mean, 10–12 years) than neurologic manifestations
  - **Cirrhosis:** symptoms may be minimal or absent with nearly normal liver biochemical tests
  - **Chronic hepatitis:** indistinguishable from viral or autoimmune chronic hepatitis
  - **Fulminant hepatic failure:** indistinguishable from viral hepatic failure

2- **Neurologic:** tends to occur in the second to third decades of life
  - **Common** symptoms, dysarthria, clumsiness, tremor, drooling, gait disturbance, mask-like facies and deterioration of handwriting are seen **early**
  - **Less often**, rigidity with overt parkinsonian features, flexion contractures, grand mal seizures, and spasticity are seen in the **later** stages of the disease
  - Cognitive ability usually remains normal regardless of severe neurologic impairment

3- **Psychiatric:** symptoms are present in almost all neurologically affected patients, and the severity tends to parallel that of the neurologic abnormalities
  - **Early** symptoms in teenagers may be limited to subtle behavioral changes and deterioration of academic and work performance
  - **Later**, patients present with personality changes, emotionalism and antisocial behavior, depression that may lead to suicidal ideation, and increased sexual preoccupation

4- **Hematological:** acute intravascular hemolysis
  - It may be the presenting features in up to **15%** of patients

- It's transient and self-limited but often associated with Fulminant hepatic failure or chronic hepatitis

5- **Ophthalmologic:** Kayser–Fleischer rings:

- A golden brown or greenish discoloration, initially at the superior and inferior corneal poles and eventually becoming circumferential
- Present in 95% of patients with neurologic manifestations and ≥ 50% of those without neurologic symptoms
- **Not pathognomonic** of WD, since they also are:
  - Absent in > 40% of patient with chronic hepatitis
  - Usually absent in children presenting with liver disease
  - Seen occasionally in patients with long-standing cholestasis (such as intrahepatic cholestasis of childhood, primary biliary cirrhosis, and partial biliary atresia).

Diagnosis

When to suspect: Individuals between ages 3 and 40 years with

1- A sibling or parent of patient diagnosed with WD
2- Unexplained elevated serum aminotransferase, fulminant hepatic failure, chronic hepatitis, or cirrhosis
3- Unexplained acquired Coombs-negative hemolytic anemia
4- Unexplained neurologic features (abnormal behavior, incoordination, tremor, dyskinesia).
5- A psychiatric disorder with signs of hepatic or neurologic disease, or being refractory to therapy
6- Kayser–Fleischer rings detected on routine eye examination

Diagnostic tests

1- **Serum ceruloplasmin** (Normally 20-40 mg/dl):

- **Low** serum ceruloplasmin occurs in most WD patients
- It may be normal in up 15% of patients with WD & hepatic involvement reflecting an acute phase response to hepatic injury
- The combination of a low serum ceruloplasmin level and Kayser–Fleischer rings is sufficient to establish a diagnosis of WD
- **A decreased level is not pathognomonic** of WD. The following non-Wilsonian causes should also be considered:
  - Diminished synthetic function as a consequence of severe liver disease
  - Nephrotic syndrome, protein-losing enteropathy, and intestinal malabsorption
  - 10–20% of asymptomatic heterozygote carriers of the WD gene (~1 per 2000 in the general population)
  - Children up to age of 2 years (physiologically low levels).
  - Hereditary aceruloplasminemia, which is unrelated to WD and associated with iron overload

2- **Free serum copper** (nonceruloplasmin-bound copper):

- Elevated (although total serum copper "ceruloplasmin-bound + nonceruloplasmin-bound" is decreased).

3- **Hepatic copper:** elevated.

The finding of a normal hepatic copper concentration excludes the diagnosis, but an elevated level alone may also be found in other liver diseases:

a) Cholestatic disorders
  - Primary biliary cirrhosis
  - Primary sclerosing cholangitis
  - Intrahepatic cholestasis of childhood
  - Biliary atresia

b) Non-Wilsonian hepatic copper toxicosis
  - Indian childhood cirrhosis
  - Idiopathic copper toxicosis

4- **Urinary copper excretion:** elevated

- The test is useful in confirming the diagnosis of WD and in monitoring compliance and response to chelation therapy
- In untreated patients, the 24-hour urinary excretion of copper reflects the amount of non-ceruloplasmin-bound copper in the circulation

5- **Liver biopsy:** only indicated if

- Clinical signs and noninvasive tests do not allow a final diagnosis
- There is suspicion of other or additional liver pathologies

6- **Genetic diagnosis:**

- DNA marker studies can be performed only within families in which the diagnosis is already established in one family member, using the index patient DNA as a reference

Treatment

Diet

1- A low copper diet is rarely prescribed or necessary

2- Tips to decrease dietary copper intake include:

- Avoid foods with a high copper content (e.g., liver, chocolate, nuts, mushrooms, legumes and shellfish)
- Use deionized or distilled water if the drinking water copper content > 0.2 ppm
- Avoid use of domestic water softeners and untested well water

Drugs

1- **D-Penicillamine:**

- **Indications:** 1st line drug in Wilson’s disease
- Jjgj
- **Mechanism:**
  - Copper chelation & detoxification→ promoting the urinary excretion of copper
  - Possibly induction of cellular metallothionein synthesis which enhances the proportion of nontoxic Cu-metallothionein

- **Dose:**
    - 750-1500 mg/day; best absorbed if taken on an empty stomach (Dosing in children is 20 mg/kg/day).
    - Adequacy of treatment can be monitored by measuring 24-hour urinary copper excretion while on treatment
    - Urinary copper excretion should run in the range of 3–8 µmol/24 hrs on treatment
- **Side-effects:**
    - Interference with pyridoxine action, supplemental pyridoxine should be provided (25–50 mg/day).
    - Interference with collagen cross-linking and has some immunosuppressant actions
    - Bone marrow suppression, significant proteinuria (>1 g/24 h) or significant worsening of neurologic features usually requires withdrawal of the drug

2- Trientine:

- **Indications:** 2nd line drug if D-Penicillamine is intolerated
- **Mechanism:**
    - Copper chelation & detoxification→ promoting the urinary excretion of copper
- **Dose:** same as D-Penicillamine
- **Side-effects:**
    - Neurological worsening after beginning of treatment
    - A reversible sideroblastic anemia
    - Iron chelation and co-administration with iron should be avoided because it forms toxic iron-complexes

3- Zinc:

- **Indications**: may be used as
    - A therapy in presymptomatic & neurologic patients

  - A maintenance therapy in patients who have been previously decoppered and in combination therapy
  - A temporary measure during pregnancy
- **Mechanism:**
  - Interference with the uptake of copper from the gastrointestinal tract by induction of intestinal & hepatic formation of metallothionein that is an endogenous chelator of metals → copper is excreted within the shed intestinal cells
- **Dose:** 150 mg elemental zinc/day (for children <50 kg in body weight 75 mg) administered in three divided doses, 30 min before meals
- **Side-effects:**
  - GIT upset
  - Elevations in serum lipase and/or amylase may occur, without clinical or radiologic evidence of pancreatitis

4- **Ammonium tetrathiomolybdate:**

- **Indication:** remains an experimental therapy, and it is not commercially available
- **Mechanism:** In the intestinal tract it prevents absorption of copper, and in the circulation it makes copper unavailable for cellular uptake
- **Side-effects:**
  - Bone marrow depression
  - Hepatotoxicity
  - Overly aggressive copper removal, which causes neurological dysfunction

Preferred drug regimen

1- **Initial therapy:**

- Treatment is initiated with D-penicillamine at a starting dose of 250-500 mg, gradually increased to 1-1.5 g/day

- Because of the potential for bone marrow suppression and nephrotic syndrome, a complete blood count and routine urine alysis should be performed every 2 weeks during the first 2 months of therapy
- Patients intolerant of D-penicillamine may be treated with trientine
- Zinc or tetrathiomolybdate may be utilized when side-effects caused by D-penicillamine are also known to be associated with trientine

2- **Maintenance therapy:**

- Once clinical symptoms and signs have stabilized, and urinary excretion of copper is < 0.5 mg/24 h or the non-ceruloplasmin copper is reduced to < 10–15 µg/dL, the dose of chelating agents should be reduced to the minimum essential dosage for maintenance
- Typical daily maintenance dosages for the current medications for adults are 750–1500 mg for penicillamine and trientine and 150 mg for zinc

3- **Pregnancy:**

- Therapy for WD patients should be continued throughout pregnancy
- D-penicillamine, trientine and zinc, all appear to be safe during pregnancy in humans
- It's recommended that dose of D-penicillamine (or trientine) should not exceed 1 g/day during pregnancy and, if cesarean section is anticipated, the dose should be reduced to 0.5 g/day 6 weeks prior to delivery and until wound healing is complete
- Maintenance therapy with zinc does not require dose adjustment during pregnancy

4- **Patients with neurological disease:**

- About 10–20% (up to 50% in one series) of patients presenting with neurologic disease have worsening of neurologic symptoms during initial treatment with D-penicillamine, this may be caused by the mobilization and redistribution of copper in the brain during initial treatment

- Treatment with D-penicillamine **should be continued** in these patients, with gradual adjustment of the dose to increase urinary copper excretion
- If neurologic manifestations continue to worsen, alternative approaches should be introduced

Liver transplantation

1- Indicated for Fulminant hepatitis and hepatic insufficiency unresponsive to medical therapy

2- Liver transplantation for refractory neurological manifestations should be considered as experimental; however, there are several reports of improvement in these patients after liver transplantation

Alpha-1 antitrypsin (α_1-AT) deficiency

Pathophysiology

1- Normally:

- α_1-antitrypsin (α_1-AT) is a protease inhibitor formed in the liver, responsible for inhibition of trypsin, collagenase, elastase and proteases of neutrophills
- It's encoded by a gene located on chromosome 14

2- In α_1-AT deficiency:

- More than 100 variants of α_1-AT deficiency are recognized. Not all variants are associated with clinical diseases
- The Z α_1-AT protein is caused by replacement of glutamic acid by lysine in position 342
- PiMM (Pi = protease inhibitor) is the phenotype present in 95% of the population & associated with normal serum levels of α_1-AT

- PiZZ and PiSZ phenotypes are associated with severe deficiency and liver disease, whereas PiMZ phenotype leads to intermediate deficiency
- Low circulating levels of α_1-AT → the function of proteases is unopposed
    - In lung → progressive decease in elastin and development of premature emphysema
    - In liver → aggregates of defective proteins are found leading to cirrhosis by unclear mechanism

Clinical features

1- **Neonatal cholestasis and jaundice**:

- Develops in 10% of homozygotes, with subsequent hepatomegaly & portal hypertension

2- **Presentation in adulthood**:

- Occur in 10% of homozygotes with cirrhosis or emphysema (rarely both in the same patients).

3- **Adults or children with liver involvement**:

- May have no symptoms until they develop signs & symptoms of chronic liver disease

4- **Emphysema**:

- Develops in 60-70% of adults with α_1-AT deficiency over the age of 25 years with the peak in the 4th and 5th decade

Diagnosis

1- **Serum α_1-AT level:**

- Is generally reduced in affected patients
- α_1-AT is an acute phase reactant, so it may be falsely elevated

2- **Phenotyping (Pi):**

- Certain heterozygous states can result in chronic liver diseases (e.g. PiSZ and PiZZ patients can develop cirrhosis).

- PiMZ heterozygotes usually don't liver diseases unless they have some other liver diseases such as alcoholic liver disease, NASH or chronic viral hepatitis

3- **Liver biopsy:**
  - Liver histology with numerous eosinophilic diastase-resistant globules which are PAS-positive (**p**eriodic **a**cid-**S**chiff) in the endoplasmic reticulum of hepatocytes, is classic for the disease
  - With diastase-PAS stain, PAS stains both glycogen and α_1-AT globules reddish purple and diastase digests the glycogen, thus the only PAS-positive globules are those of α_1-AT

Treatment

1- **No specific therapies** are available for α_1-AT deficiency at these times

2- **Symptomatic management:**
  - Infant with cholestasis may benefit from fat-soluble vitamins (A, D, E and K).
  - Ursodeoxycholic acid may increases bile flow and reduce liver injury associated with cholestasis

3- **Liver transplantation** is recommended for end-stage liver disease

Family screening

1- **Target population:**
  - First-degree relatives & siblings of α_1-AT deficiency patients

2- **Screening tests:**
  - Serum level of α_1-AT
  - Phenotyping to identify PiSZ and PiZZ family members

Liver transplantation

Indications

Liver transplantation should be considered in patients with irreversible liver failure resulting from acute or chronic liver diseases, as well as hepatocellular malignant diseases

1- Noncholestatic or inflammatory

- Chronic hepatitis C
- Chronic hepatitis B
- Alcoholic liver disease
- Autoimmune hepatitis
- Nonalcoholic fatty liver disease
- Cryptogenic cirrhosis
- Drug-induced liver injury
- Sarcoidosis

2- Cholestatic

- Primary biliary cirrhosis
- Primary sclerosing cholangitis
- Secondary biliary cirrhosis
- Idiopathic adulthood ductopenia

- Cystic fibrosis
- Familial intrahepatic cholestasis syndromes

3- **Metabolic**

- Alpha-1 antitrypsin deficiency
- Hereditary hemochromatosis
- Wilson disease
- Glycogen storage disease

4- **Malignant**

- HCC
- Neuroendocrine tumors
- Epithelioid hemangioendothelioma
- Fibrolamellar HCC

5- **Extrahepatic**

- Familial amyloidosis
- Primary hyperoxaluria
- Homozygous familial hypercholesterolemia

6- **Miscellaneous**

- Acute liver failure
- Budd–Chiari syndrome
- Polycystic liver disease
- Giant cavernous hemangioma
- Noncirrhotic portal hypertension
- Retransplantation

Contraindications

1- Relative contraindications:

- Poor nutritional status
- High body mass index
- Poorly controlled chronic illnesses such as diabetes mellitus
- Portal and mesenteric thromboses
- Inadequate management of psychiatric disorders
- Past history of malignant disease

2- Absolute contraindications:

- Severe cardiopulmonary disease
- Infection
- Psychosocial concerns

Contraindications

1- Active uncontrolled infection or sepsis
2- Severe neurologic compromise, including brain death
3- Cardiovascular disease
    - Severe or symptomatic coronary artery disease
    - Heart failure
    - Valvular disease
4- Pulmonary disease
    - Chronic obstructive pulmonary disease with oxygen dependence
    - Pulmonary fibrosis
    - Severe pulmonary hypertension
5- Concurrent extrahepatic malignant disease
6- Lack of psychosocial support or inability to comply with treatment regimen
7- Active alcohol or substance abuse
8- Anatomic abnormalities precluding liver transplantation
9- Compensated cirrhosis without complications (Child–Pugh class A)
10- HIV

Post-transplant complications

1- Primary graft non-function

- Occurs in the immediate postoperative period
- Characterized by progressive elevations in serum aminotransferase levels and worsening coagulopathy in the absence of vascular abnormalities
- It may require repeat transplantation

2- Hepatic artery thrombosis or stenosis

- It is associated with biliary complications resulting from ischemic injury
- U/S may be useful in the diagnosis
- Angioplasty or stent placement for stenosis

3- Biliary tract complications

- Occur in: up to 25% of liver transplant recipients, typically within the first year
- Strictures: are the most common biliary complication
  - Most biliary strictures (80%) are anastomotic
  - Nonanastomotic strictures are strongly associated with hepatic artery thrombosis
- Arterial patency: should be assessed during the evaluation of a suspected biliary stricture

4- **Allograft rejection**

- Acute cellular rejection:
  - Common, occurring in up to 40% of patients
  - Does not have a major impact on post-transplant survival, although it is associated with significant morbidity
  - Presenting with fever within 5-10 days of transplantation
  - Treated with immunosuppressive drugs
- Chronic rejection:
  - Characterized histologically by ductopenia
  - May result in progressive allograft dysfunction and the potential need for repeat transplantation
  - Occurs within 6 weeks to 9 months of transplantation

5- **Infections**

- Bacterial, viral and fungal infections: are common following liver transplantation as a consequence of immunosuppressive therapy
- Cytomegalovirus (CMV) infection: (® see infections)
  - Is most common in CMV-seronegative recipients of CMV-seropositive allografts
  - Infection may be associated with pancytopenia and may result in severe disseminated disease, hepatitis, enterocolitis, or pneumonitis

- Herpes simplex virus: may become reactivated in the setting of immunosuppression (® see infections).
- Epstein–Barr virus: is associated with the development of post-transplant lymphoproliferative disorder, which may occur in the setting of primary infection or reactivation (® see infections).
- Opportunistic fungal infections: (® see infections)
- Antimicrobial prophylaxis regimens and immunization: are required following liver transplantation to minimize the risk of serious nosocomial, community-acquired, and opportunistic infections
- Use of oral nucleoside or nucleotide analogue and hepatitis B immune globulin (HBIG) following liver transplantation decreases the rate of recurrent HBV infection and improving post transplant survival

6- Renal failure

- Common.
- Typically due to long-term calcineurin inhibitor therapy
- Use of sirolimus is useful (no nephrotoxicity).

7- Recurrent disease

- Recurrent hepatitis C:
    - May result in allograft dysfunction, progressive fibrosis, and ultimately allograft failure
    - Liver biopsies should be done at regular intervals to assess for recurrent disease and the need for antiviral therapy
- Following liver transplantation for HCC: close surveillance should be considered, particularly in patients who exceed the Milan criteria (increased potential for Recurrence).
- Autoimmune or genetic: autoimmune hepatitis, NAFLD with steatohepatitis, PBC, and PSC

8- Malignant disease

- Increased risk of de novo extrahepatic malignant diseases, including post-transplant lymphoproliferative disorder and skin, colorectal, and gynecologic cancers
- Close surveillance with standard cancer screening tests is recommended

9- **Post- transplant metabolic syndrome**

- The development of hypertension, hyperlipidemia, obesity, and diabetes mellitus are common following liver transplantation
- These complications result from the combined effects of corticosteroids and immunosuppressive medications
- The risk of cardiovascular events and associated mortality may be increased

Liver transplant evaluation

1- Hepatology and transplant surgery **consultations**

2- **Extensive laboratory testing** for accurate assessment of current clinical status, evaluation of potential causes of underlying chronic liver disease, and screening for comorbid illnesses

3- **Important investigations:**

- ABO blood grouping
- HLA typing
- Patent hepatic artery and portal vein

4-Accurate assessment of **renal function**

5- **Imaging for surveillance** for HCC, assessment of hepatic vasculature, and evaluation of hepatic anatomy

6- **Cardiopulmonary evaluation**, which may include right or left heart catheterization, depending on risk factors

7- **Psychosocial assessment**

8- **Age-appropriate screening tests** including colonoscopy, mammogram, PSA level, and Pap test

Referral to a liver transplant center

1- Patients with evidence of **decompensated liver disease** reflected in elevated MELD or CTP scores

2- Patients who develop **complications** such as hepatic encephalopathy, variceal bleeding, ascites with or without spontaneous bacterial peritonitis, or renal insufficiency

Assessment of liver disease severity

1- Important for 2 reasons

- Determining the appropriate timing for referral to a liver transplant center
- Key factor in prioritization for transplantation

2-Child–Turcotte–Pugh scoring system and Child–Pugh Classification Points

	1	2	3
Ascites	None	Slight-moderate	Tense
Encephalopathy grade	0	1–2	3–4
Serum albumin level (g/dL)	>3.5	2.8–3.5	<2.8
Serum bilirubin level (mg/dL)	<2	2-3	> 3
INR	<1.7	1.7–2.3	>2.3
(or PT above normal)	(<4)	(4 to 6)	(>6)

- This score was developed to predict operative mortality in persons with cirrhosis who required portacaval shunt surgery for variceal bleeding
- Child–Pugh classes B and C are associated with a survival benefit following liver transplantation
- This score was previously used for allocation of donor organs and is still widely used to predict the risk of perioperative mortality in cirrhotic patients undergoing surgery
- Child–Pugh class (Child- Turcotte-Pugh score)
    - A → (5–6)
    - B → (7–9)

- C → (10–15)

3- **Model for End-stage Liver Disease (MELD)**

MELD score = 9.57 × loge (serum creatinine [mg/dL]) + 3.78 × loge (serum bilirubin [mg/dL]) + 11.20 × loge (INR) + 6.43

- The MELD was initially developed to predict 3-month mortality in patients undergoing TIPS placement
- It is superior to the CTP score in predicting short-term (3-month) mortality in patients with ESLD
- It was introduced in 2002 as the basis for allocation of donor organs in the United States

4- **Clinical stages of cirrhosis and mortality risk**

Stage	Complications	1-yr mortality risk %
1	No varices, No ascites	1%
2	Varices present, No ascites	3.4%
3	Ascites present	20%
4	Variceal hemorrhage	57%

- By Baveno IV consensus
- The risk of clinical decompensation and progression from compensated ESLD to a more advanced stage is approximately 10% per year

The Milan criteria

1- Define the tumor size that is acceptable for liver transplantation:

- If one solitary lesion is found, it must be < 5 cm in greatest diameter
- If two or three lesions are present, each must be < 3 cm in greatest diameter
- The absence of vascular invasion of tumor and of evidence of extrahepatic metastases must be ascertained

Criteria for UNOS Status 1A designation in acute liver failure

1- Age >18 yr

2- Life expectancy without liver transplantation of <7 days

3- Onset of encephalopathy within 8 wk of the first symptoms of liver disease

4- Absence of preexisting liver disease

5- Admission to an intensive care unit and one of the following:

  - Ventilator dependence
  - Requirement for renal replacement therapy
  - INR >2.0

6- Fulminant Wilson disease

Donor selection criteria

1- Adequate allograft volume, to prevent small-for-size syndrome:

  - Volume should be at least 35% to 40% of normal liver size for the recipient
  - The minimum percentage of allograft to body weight is 0.8%.

2- ABO compatibility

3- Absence of significant liver fibrosis or steatosis (less than 20% to 30%)

4- Donor age < 60 years

5- Confirmed brain death

6- Absence of evidence of bacterial or fungal infection

7- Absence of risk factors for, or evidence of, chronic viral hepatitis or HIV infection

8- Absence of significant comorbid conditions such as diabetes mellitus, obesity, or extrahepatic malignant disease

Immunosuppression after liver transplantation

1- Corticosteroids

  - Action:
    - Inhibit complement and antibody-mediated immunity as well as production of cytokines, including interleukin (IL)-1, IL-2, and interferon gamma
  - Value:

  - They are an important component of liver transplant immunosuppression as induction agents, in maintenance therapy, or in the treatment of allograft rejection
- Side effects:
  - Diabetes mellitus
  - Hypertension
  - Hyperlipidemia
  - Increased risk of osteoporosis.

2- Cyclosporine and Tacrolimus

- Action:
  - Calcineurin inhibitors block transcription and production of IL-2 and lead to inhibition of T-cell activation.
- Value:
  - Tacrolimus is the most common immunosuppressive agent used following liver transplantation
- Side effects:
  - Nephrotoxicity
  - Neurotoxicity
  - Hypertension
  - Diabetes mellitus
  - Hyperlipidemia.
- Drugs are metabolized through the cytochrome P-450 system; therefore, blood levels are affected by medications that induce or inhibit cytochrome P-450 metabolism

3- Mycophenolate mofetil and Mycophenolic acid

- Action:
  - These antimetabolites inhibit lymphocyte activation through disruption of purine synthesis
- Value:

        - Typically used in maintenance regimens in combination with other agents
    - Side effects:
        - Myelosuppression
        - Gastrointestinal symptoms
        - No nephrotoxicity

4- Sirolimus

- Action:
    - Inhibits cytokine-mediated signaling pathways and lymphocyte cell cycle progression and leads to decreased cellular activation and proliferation
- Value:
    - May be used as an alternative agent in patients with renal failure
- Side effects:
    - Hyperlipidemia
    - Myelosuppression
    - Gastrointestinal symptoms
    - Delayed wound healing
    - Possibly hepatic artery thrombosis
    - No nephrotoxicity

5- Antibody therapy

- Action:
    - **Antithymocyte globulin** is a polyclonal antibody directed against T cells that leads to their depletion
    - **OKT-3** is a monoclonal antibody that binds to CD3, inactivates the T-cell receptor, and leads to lymphocyte depletion
- Value:
    - Monoclonal antibodies directed against the IL-2 receptor—daclizumab and basiliximab—are used increasingly as induction agents in corticosteroid-sparing regimens

    - polyclonal antibody may be used as induction therapy or in the management of acute allograft rejection
- Side effects:
    - Profound myelosuppression

Acute liver failure

Definition

1. Syndrome characterized by a rapid decline in hepatic synthetic function and a significant risk of mortality
2. ALF is defined by the onset of jaundice, hepatic encephalopathy, and coagulopathy (INR of prothrombin time > 1.5) in patients with no prior history of liver disease

Classification

1. **From the onset of jaundice to encephalopathy** (O'Grady):
    - Hyperacute liver failure: interval < 7 days
    - ALF: interval from 8 - 28 days
    - Subacute liver failure: interval from 29 days - 12 weeks
2. **A hyperacute presentation** is associated with
    - Acetaminophen hepatotoxicity or fulminant hepatitis A or B
    - Better prognosis
    - Increased incidence of cerebral edema
    - Absence of clinical jaundice

Causes of acute liver failure

1. **Viral hepatitis**
    - Hepatitis A, B, C, D, and E viruses
    - Herpes viruses 1, 2, and 6
    - Varicella zoster virus
    - Adenovirus
    - Epstein–Barr virus
    - Cytomegalovirus
    - Parvovirus B19
2. **Drug-induced liver injury**
    - Acetaminophen overdose
    - Idiosyncratic drug reactions
    - Cocaine
    - Ecstasy (methylenedioxymethamphetamine [MDMA])
3. **Toxins**

  - Amanita or Galerina mushroom poisoning (Amanita phalloides most common)
  - Organic solvents
  - Phosphorus

4- **Metabolic disorders**

  - Acute fatty liver of pregnancy
  - Reye's syndrome

5- **Vascular events**

  - Acute circulatory failure, ischemic hepatitis
  - Budd–Chiari syndrome
  - Sinusoidal obstructive syndrome
  - HELLP syndrome
  - Heat stroke

6- **Miscellaneous causes**

  - Wilson disease
  - Autoimmune hepatitis
  - Giant cell hepatitis
  - Malignancy with liver infiltration
  - Liver transplantation with primary graft nonfunction

Common causes

1- **The most common** identifiable causes of ALF are drug induced liver injury and acute viral hepatitis

2- **Pregnancy-related** acute liver failure includes acute fatty liver of pregnancy and the hemolysis, elevated liver enzymes, and low platelets (HELLP) syndrome

Cause	Frequency (%)
Acetaminophen overdose	46
Indeterminate	14

Idiosyncratic drug-induced liver injury	11
Hepatitis B	8
Autoimmune hepatitis	6
Ischemic hepatitis	4
Hepatitis A	3
Wilson disease	2
Budd–Chiari syndrome	1
Pregnancy*	1
Other	5

Clinical features

1- **History:** may suggest potential causes of ALF including exposure risks, a history of depression or suicidal ideation, illicit drug or alcohol abuse, or ingestion of hepatotoxic agents

2- **Changes in mental status** (encephalopathy) with no previous liver disease or precipitating factors

  - Lethargy, drowsiness, coma
  - Reversal of sleep patterns
  - Personality changes

3- **Cerebral edema** (usually without papilledema)

4- **Coagulopathy** (prolonged prothrombin time; [INR] 1.5 or more)

5- **Jaundice**

6- **Multiple organ failure**

  - Acute respiratory distress syndrome
  - Cardiac arrhythmias
  - Hepatorenal syndrome
  - Metabolic acidosis
  - Sepsis
  - Gastrointestinal bleeding
  - Hypotension

7- **Development of ascites and anasarca**

8- Serial physical examination showing shrinking liver and progressive jaundice

9- Drug or toxin induced ALF (important part ®)

10- Other causes: write in brief

11- Complications: write in brief

Laboratory features of ALF

1- **Striking coagulopathy** with prolonged prothrombin time (INR 1.5 or more)

2- Leukocytosis

3- Hyponatremia, and hypokalemia are common

4- Hypoglycemia

5- Marked elevations of serum **bilirubin and aminotransferase** levels, but the latter may decline toward normal despite disease progression

6- Mild to moderate **hypoalbuminemia**

Complications

1- Infection

- 80% of patients may develop bacterial infections (due to ↓complement), and up to 30% may develop fungal infections
- Surveillance cultures: of blood, sputum, and urine should be obtained
- Antimicrobial prophylaxis: have no impact on clinical outcome but empiric therapy should be initiated in the following circumstances:
  - Positive surveillance culture or fever
  - Grade 3 to 4 encephalopathy
  - Hemodynamic instability or the onset of SIRS
  - Patients listed for liver transplantation

2- Renal failure

- This is a key early prognostic indicator, particularly in patients with acetaminophen hepatotoxicity, in which renal failure or the presence of acidosis is highly predictive of mortality
- Cause: hypovolemia, acute tubular necrosis, or hepatorenal syndrome
- Prevention: Use of vasopressor therapy with norepinephrine or dopamine in circulatory dysfunction with severe hypotension

- Renal replacement therapy: with continuous venovenous hemodialysis (CVVHD) is preferred once renal or circulatory dysfunction develops

3- **Metabolic disorders**

- Contribute to progressive hepatic encephalopathy and an increased risk of cerebral edema; therefore, they must be corrected promptly
- Hypoglycemia:
  - May result from decreased hepatic glycogen production and impaired gluconeogenesis
  - Blood glucose levels must be measured at frequent intervals
  - Continuous infusions of 10% to 20% glucose if hypoglycemia
- Hypophosphatemia
  - May be seen in ALF as a result of ATP consumption in the setting of rapid hepatocyte regeneration, which has been reported to be associated with a more favorable prognosis
  - Life-threatening hypophosphatemia can occur, and phosphorus levels should be monitored frequently and repleted promptly
- Acidosis
  - One of the most important predictors of mortality
  - Metabolic acidosis with a pH < 7.3 may be associated with a mortality rate of up to 95% in patients with acetaminophen overdose in the absence of liver transplantation
  - Give NaHCO3
- Alkalosis: may be present; hyperventilation is common
- Hypoxemia:
  - Due to ARDS, aspiration, or pulmonary hemorrhage
  - Patients with grade 3 to 4 encephalopathy should undergo endotracheal intubation
- Hypokalemia:
  - Due to diuretics and glucose infusion
  - Treated by KCL 10-15 gm/d

- Hyponatremia: due to ↓ free H_2O excretion

4- **Coagulopathy**

- Coagulopathy is a key feature of ALF and is an important prognostic indicator
- Although coagulopathy can be profound, serious bleeding are uncommon
- Proton pump inhibitors or H2-receptor blockers: should be administered to all patients because of the potential for gastrointestinal bleeding with progressive coagulopathy and the risk of peptic ulcer associated with mechanical ventilation
- Platelet transfusions, plasma, and cryoprecipitate: may be given to reduce the bleeding risk associated with invasive procedures
- Correction of coagulopathy is otherwise not recommended unless clinically significant bleeding occurs
- Administration of recombinant factor VIIa may be considered, although it may be associated with an increased risk of thrombosis
- Vitamin K may be given if nutritional deficiency is suspected

5- **Encephalopathy**

- Encephalopathy is the defining feature of ALF and may progress rapidly, leading to increased risks of cerebral edema, intracranial hypertension, and death
- The risk of cerebral edema increases with the severity of encephalopathy; up to 35% and 75% of patients develop cerebral edema at encephalopathy grades 3 and 4, respectively
- CT of the head: considered in grades 3 or 4 encephalopathy to assess for cerebral edema or intracranial bleeding
- Lactulose therapy: no significant impact on outcome, particularly with an advanced grade of encephalopathy

6- **Cerebral edema**

- Cerebral edema with intracranial hypertension is the most common cause of mortality in ALF
- Hyperacute course: are at greater risk of developing cerebral edema
- Elevated arterial ammonia levels > 200 μmol/L: may predict an increased risk of developing intracranial hypertension
- Factors contributing to cerebral edema: include hypoxia, systemic hypotension, decreased cerebral perfusion pressure (CPP), and swelling of astrocytes as a result of elevated blood ammonia levels and increased glutamine production within the brain
- Cerebral edema may lead to: increased intracranial pressure (ICP), ischemic brain injury, and herniation
- Intracranial hypertension findings: abnormal papillary reflexes, muscular rigidity, or decerebrate posturing

Management of cerebral edema

a). General

- Reduction of surrounding stimuli to a minimum
- Elevation of head of bed to 30 degrees
- Endotracheal intubation and sedation at grade 3 encephalopathy
- Initiation of vasopressor therapy and CVVHD if circulatory dysfunction or renal failure

b). Specific

- Consider placement of ICP monitor
    - * Goal ICP <25 mm Hg and CPP >50 mm Hg
- Initiation of hyperventilation-induced hypocapnea to promote cerebral vasoconstriction
    - * Goal Pco2 30 to 40 mm Hg
- Intravenous mannitol
    - * 0.25 to 0.5 g/kg bolus for ICP ≥25 mm Hg for >10 min
    - * Repeat infusions for persistent ICP elevations
    - * Maintain serum osmolality <320 mOsm/L

Treatment

1- Initial laboratory and imaging assessment of ALF

- Routine: complete metabolic profile, PT/INR, CBC; amylase, lipase, ceruloplasmin, factor V level, pregnancy test, urinalysis, blood type and screen, surveillance cultures
- Arterial blood gas; arterial blood lactate, arterial ammonia levels
- Urine toxicology screen, acetaminophen level
- Autoimmune hepatitis markers: ANA, SMA, quantitative immunoglobulins
- Viral serologic tests: IgM anti-HAV, IgM anti-HBc, HBsAg, anti-HCV, IgM anti-HEV, IgM anti-HSV 1 and 2, IgM anti-VZV, HIV test
- Imaging: abdominal ultrasonography (may show hepatic surface nodularity associated with parenchymal collapse and regenerative nodule formation) with Doppler, chest radiography, CT scan of the head (if grade 3 to 4 encephalopathy)
- Additional studies:
    - Viral hepatitis PCR: HBV DNA, HSV DNA, HCV RNA, EBV DNA, CMV DNA, VZV DNA, adenovirus DNA
    - Serum copper, 24-hr urine copper levels
- Liver biopsy: not indicated except in suspected autoimmune hepatitis, acute herpes simplex hepatitis or malignant disease (Transjugular approach)

2- Intensive care management of ALF:

- Patients should be transferred to an intensive care unit once the presence of encephalopathy is established
- Hemodynamic monitoring (arterial line, central venous and pulmonary artery catheters)
- Endotracheal intubation (grade 3 to 4 encephalopathy)
- Renal replacement therapy (CV VHD)
- Neurologic monitoring
- Glucose monitoring for hypoglycemia

- Laboratory parameter assessment at frequent intervals, correction of metabolic derangements
- Enteral nutrition
- Periodic surveillance bacterial and fungal cultures (blood, sputum, urine)
- Medications:
  - Proton pump inhibitor or H2-receptor blocker
  - Empiric antimicrobial therapy with infection risk
  - 10%–20% glucose infusions if hypoglycemia present
  - Vasopressor management for circulatory dysfunction
- Management of cerebral edema and consideration of ICP monitoring

3- Specific therapy according to the cause of ALF

Cause	Treatment
Acetaminophen hepatotoxicity or any cause of ALF with mild to moderate Encephalopathy (grade 1-2)	N-acetylcysteine - Intravenous (preferred): loading dose 150 mg/kg in 5% dextrose over 1 hr, then 12.5 mg/kg/hr over 4 hr, then 6.25 mg/kg/hr - Oral: loading dose 140 mg/kg, then 70 mg/kg every 4 hr
Amanita phalloides poisoning	- Gastric lavage and administration of activated charcoal - Intravenous penicillin G 1g/kg/day
Herpes simplex hepatitis	Intravenous acyclovir 30 mg/kg/day
Cytomegalovirus infection	Intravenous ganciclovir 5 mg/kg every 12 hr
Acute hepatitis B	Oral nucleoside or nucleotide analogue (entecavir 0.5 mg/day or tenofovir 300 mg/day preferred)
Autoimmune hepatitis	Intravenous methylprednisolone 60 mg/day
Acute fatty liver of pregnancy or HELLP syndrome	Delivery of the fetus
Budd–Chiari syndrome	Anticoagulation therapy and consideration of TIPS placement

- Establishing the potential cause of ALF guides the utilization of specific therapies, some of which may have a significant impact on outcome

- Prospective data demonstrated that administration of *N*-acetylcysteine (NAC) may provide a survival benefit in cases of non–acetaminophen-associated ALF with grade 1 or 2 encephalopathy; therefore, NAC is recommended for all patients with mild to moderate hepatic encephalopathy, regardless of cause, until there is evidence of improved hepatic function
- In acetaminophen hepatotoxicity, restoration of hepatocyte glutathione synthesis depends on cysteine, which may be administered in the form of NAC; NAC should be given in all cases of suspected acetaminophen overdose regardless of serum acetaminophen level

4- Assessment of prognosis in acute liver failure (King's College criteria)

ALF 2ry to acetaminophen overdose	**ALF not associated with acetaminophen**
- pH <7.30 Or - INR >6.5 (PT >100 sec) and serum creatinine >3.4 mg/dL (>300 µmol/L) in patients with grade 3 or 4 encephalopathy	- INR >6.5 (PT >100 sec Or - Any 3 of the following: * Age <10 and >40 yr * Cause non-A, non-B hepatitis or idiosyncratic drug reaction * Duration of jaundice before encephalopathy >7 days * INR >3.5 (PT >50 sec) * Serum bilirubin >17.6 mg/dL (>300 µmol/L)

- King's College criteria provides high specificity for mortality however, failure to fulfill the criteria does not ensure survival
- ALT, AST not useful for prognosis because they decrease with progressive liver damage

5- Overview on treatment

- Liver transplantation:
  - Should be considered in all patients, and contact should be made with liver transplant center early during the clinical course
  - Overall 3-year survival rate up to 78%

- Contraindications to liver transplantation in ALF
  Severe cardiopulmonary disease or multiorgan failure
  Septic shock
  Extrahepatic malignant disease
  Extensive thrombotic disease
  Irreversible brain injury or brain death [CPP < 40 mm Hg for more than 2 hours & Sustained ICP > 50 mm Hg]
  Active substance abuse, repeated suicide attempts, or inadequate social support
- Patients with ALF who are at high risk of mortality and who fulfill listing criteria defined by the United Network for Organ Sharing (UNOS) may be assigned to category Status 1A and receive top priority for liver transplantation allocation; patients with fulminant Wilson disease also may be given Status 1A priority because of the high mortality rate associated with this diagnosis

- Further therapies
  - Extracorporeal hepatic assist devices
  - Auxiliary liver transplantation, and hepatocyte culture systems : have no significant impact on survival
  - Bioartificial liver support: such as the Molecular Adsorbents Recirculating System (MARS), until native liver recovers spontaneously or until alive donor is available
- Other prognostic criteria predictive of mortality in ALF include
  - The cause: is the most important prognostic criteria
    Acetaminophen toxicity has 68% favourable rate of spontaneous recovery
    Hepatitis A has 65% favourable rate of spontaneous recovery

- Clichy criteria: The presence of hepatic encephalopathy and a factor V level < 20% of normal in patients < 30 years old or < 30% of normal in patients ≥ 30 years old predict mortality in ALF
- MELD score: at least 30 predict mortality
- APACHE II score: higher than 15 to 20 predict mortality

ACUTE HEPATITIS

Acute viral hepatitis

Hepatotropic viruses	Non-hepatotropic viruses
HAV	1- CMV (less common)
HBV	2- EBV (less common)
HCV	3- HSV (rare)
HDV	4- Yellow fever virus (rare)
HEV	[see infection] ®

HAV

1- **Type of the virus:** picorna virus (sub-classified hepatovirus), RNA

2- **Incubation period:** 15 to 50 days (average, 30 days)

3- **Period of infectivity:** HAV excreted in stools of infected persons for 1 to 2 weeks before and for at least 1 week after onset of illness, Prolonged fecal excretion (months) reported in infected neonates

4- **Viremia:** short-lived, usually < 3 weeks; occasionally up to 90 days in protracted or relapsing infection

5- **Mode of transmission:** fecal–oral transmission predominantly by person-to-person household spread; occasional outbreaks linked to common-source vehicles: (Contaminated food, bivalve mollusks, water)

6- **Other risk factors including exposure:**

- In day care centers for infants, diapered children
- In institutions for developmentally disadvantaged
- Through international travel to developing countries
- Through oral–anal homosexual behavior or multiple sexual contacts

7- **Maternal–neonatal transmission:** No

8- **Age:** children and young

9- **Acute liver failure:** Increased disease severity in individuals with preexisting liver disease or age ≥ 40 years old (fulminant in 0.5% of cases)

10- **Malignancy:** No

11- **Chronic hepatitis:** No

12- **Carrier:** No

13- **Recovery:** complete clinical, histologic and biochemical recovery within 3-6 months

HEV

1- **Type of the virus:** Hepeviridae (hepevirus), RNA

2-**Incubation period:** 40 days (range, 15 to 65 days)

3- **Period of infectivity:** HEV RNA in serum and stool during acute phase

4- **Viremia:** Prolonged viremia or fecal shedding unusual; continued viral shedding possible in rare cases in organ transplant recipients in whom chronic hepatitis develops

5- **Mode of transmission:** mainly fecal–oral transmission, intrafamilial 2ry cases uncommon

6- **Genotypes 1 and 2:** isolated from sporadic human cases and water-borne outbreaks

7- **Maternal–neonatal transmission:** documented

8- **Age:** Most common form of sporadic hepatitis in young adults in the developing world

9- **Acute liver failure:** increased risk in pregnant women with HEV infection or those with preexisting liver disease

10- **Malignancy:** No

11- **Chronic hepatitis:** no, but rare cases of chronic HEV infection in immunosuppressed organ transplant recipients

12- **Carrier:** No

13- **Recovery:** complete within 3-6 months

HBV

1- **Type of the virus:** Hepadnaviridae (DNA)

2- **Incubation period:** 15 to 180 days (average, 60 to 90 days)

3- **Period of infectivity:**

- HBV present in blood, semen, cervicovaginal secretions, saliva, and other body fluids
- Risk of HBV infection highly correlated with HBV DNA level and presence of HBeAg

4- **Viremia:** High viremia lasting for weeks to months after acute infection

5- **Mode of transmission:**

- Blood-borne transmission
  - Transfusion of blood/blood products
  - Injecting drug users
  - Hemodialysis recipients
  - Health care and other workers exposed to blood
- Sexual transmission
- Tissue penetrations (percutaneous) or permucosal transfer
  - Needlestick accidents
  - Reuse of contaminated medical equipment
  - Shared razor blades
  - Tattoos
  - Acupuncture, body piercing

- Shared toothbrushes
- No evidence of fecal–oral transmission

6- **Risk factors:** no risk factors identified in 25% of cases

7- **Maternal–neonatal transmission:** yes plus maternal-infant transmission

8- **Age:** any (more in adults)

9- **Acute liver failure:** ≤ 1% of acute infections

10- **Malignancy:** may occur

11- **Chronic hepatitis and carriers:** [risk of persistent infection is age dependent and ↓ progressively with ↑ age]

- 1% to 5% of infected adults
- 50% of infected infants
- 90% of infected neonates

12- **Carrier:** < 1% in the United States, 5% to 15% in Asia and sub-Saharan Africa

13- **Persistent infection:** [HBsAg +ve ± active HBV replication]

- Asymptomatic, inactive carrier with normal or nonspecific liver histologic changes
- Linked to chronic hepatitis, cirrhosis, HCC, and premature mortality
- Linked to acute necrotizing vasculitis, membranous glomerulonephritis, polyarteritis nodosa and less certainly mixed cryoglobulinemia

HDV

1- **Type of the virus:** Defective RNA virus requiring helper function of HBV for its expression and pathogenicity but not for its replication

2- **Incubation period:** 4 to 7 weeks

3- **Viremia:** short-lived (acute infection) or prolonged (chronic infection)

4- **Mode of transmission:** as HBV

5- **Risk factors:** HDV infections occurring solely in individuals at risk for HBV infection (coinfections or superinfections)

6- **Maternal–neonatal transmission:** yes, but frequency uncertain

7- **Acute liver failure:** more common in super-infection of HBV infected individuals than in co-infection

8- **Chronic hepatitis:** super-infection of HBV infected individuals may cause chronic HDV infection and cirrhosis

9- **Recovery:** HDV/HBV acute co-infection usually self limited and resolved without sequelae

HCV

1- **Type of the virus:**

- Flaviviridae (hepacivirus), single stranded RNA
- 6 genotypes with type 1 representing 70-80% of cases

2- **Incubation period:** 15 to 160 days (major peak at approximately 50 days)

3- **Period of infectivity:** the virus has low conc. In blood than HBV

4- **Viremia:** Prolonged viremia and persistent infection common (55% to 85%) and elevated, fluctuating or normal serum aminotransferase levels are common

5- **Mode of transmission:**

- Blood-borne transmission (the predominant mode)
  - Injecting drug use
  - Recipients of blood/blood products
  - Hemodialysis recipients
  - Tattoos; body piercing
  - Health care workers
  - Cocaine snorting
- Sexual transmission: low efficiency, low frequency
- No evidence of fecal–oral transmission

6- **Risk factors:** No recognized risk factor in 10% of cases

7- **Maternal–neonatal transmission:** low efficiency, low frequency

8- **Acute liver failure:** very rare

9- **Malignancy:** limited to those with bridging fibrosis and cirrhosis

10- **Persistent infection:** linked to chronic hepatitis (50% of cases), cirrhosis, HCC and premature death

11- **Carrier** (seroprevalance of past/present infection):

- 1.3% in USA, 20% in Italy and Japan and 40% in Egypt

12- **Recovery:**

- Self limited infections in 15-45% (higher numbers in infected children)
- Spontaneous resolution more frequent in symptomatic cases and in persons with CC genotype (IL 28B)

13- HCV infection associated with:

- Mixed cryoglobulinemia
- Cutaneous vasculitis
- Membranoproliferative glomerulonephritis
- DM type 3
- Porphyria cutanea tarda
- B-cell non-Hodgkin's lymphoma

Clinical features

1- The spectrum of severity ranges from asymptomatic, inapparent infection to fatal acute liver failure

2- Severity is increased in those with preexisting liver disease or ≥ 40 years old

Self-limited disease

1- Non- icteric hepatitis:

- Usually mild and may pass unnoticed
- Serum bilirubin < 2.5-3 mg with increased transaminases
- Clinically: mild flu-like illness with anorexia and nausea

2- Icteric hepatitis

- Pre-icteric phase:
  - Nonspecific constitutional and gastrointestinal symptoms
  - About 1-2 weeks due to viremia
  - Malaise, anorexia, nausea, and vomiting
  - Flu-like symptoms: of pharyngitis, cough, coryza, photophobia, headache, and myalgias

- Onset of symptoms: tends to be abrupt for HAV and HEV; in the others, onset is usually insidious
- Fever: is uncommon except in HAV infection
- Pain in right hypochondrium
- Immune complex mediated syndrome: which resembles serum sickness occurs in < 10% of patients with HBV infection (rarely in others) → polyarthritis, polyarthralgias, angioedema, urticaria, maculopapular eruptions, purpura, petechiae & rarely hematuria and proteinuria or cutaneous or systemic vasculitis
- Prodromal symptoms abate or disappear: with onset of jaundice, although anorexia, malaise, and weakness may persist
- If you suspect: confirm by increased ALT

- Icteric phase
  - lasts for 1 to 3 weeks
  - Swelling of hepatocytes leading to obliteration of bile canaliculus which result in intrahepatic cholestasis and jaundice
  - Dark urine
  - Clay stool color
  - Improvement of fever and headache
  - Pruritus (usually mild and transient) may occur as jaundice increases
  - Mild hepatomegaly with slight tenderness
  - Mild splenomegaly and posterior cervical lymphadenopathy are noted in 15% - 20% of patients
- Convalescent phase
  - May last for months
  - Jaundice and symptoms abate and general condition improves
  - HBsAg, HBeAg, and HBV DNA disappear
  - SGOT: decreases with the onset of recovery
  - Serum bilirubin decreases but jaundice persists for a time as bilirubin has a high affinity to collagen fibers in sclera

Acute liver failure

1- **Changes in mental status** (encephalopathy)

  - Lethargy, drowsiness, coma
  - Reversal of sleep patterns
  - Personality changes

2- **Cerebral edema** (usually without papilledema)

3- **Coagulopathy** (prolonged prothrombin time; [INR] 1.5 or more)

4- **Jaundice**

5- **Multiple organ failure**
  - Acute respiratory distress syndrome
  - Cardiac arrhythmias
  - Hepatorenal syndrome
  - Metabolic acidosis
  - Sepsis
  - Gastrointestinal bleeding
  - Hypotension

6- Development of **ascites** and anasarca

7- Serial physical examination showing **shrinking liver and progressive jaundice**

8- **Complications:** write in brief

9- **Case fatality rate** approximately 60% - 80% without liver transplantation; 1-year survival rate with liver transplantation approximately 65% - 75%

10- **Extraordinarily high frequency**, approaching 10% - 20%, in pregnant women with hepatitis E, particularly during the third trimester; high maternal and fetal mortality

Cholestatic hepatitis [due to unresolved swelling of hepatocytes]

1- Most commonly seen in **HAV** infection

2- **Pruritus** possibly prominent

3- Persistent anorexia and diarrhea in a few patients

4- **Jaundice** possibly striking and persistent for several months before complete resolution

5- **Excellent prognosis** for complete resolution without specific therapy

Relapsing hepatitis

1- Recurrence may occur **weeks to months** after improvement or apparent recovery
2- Most commonly seen in **HAV** infection; IgM anti-HAV may remain positive, and HAV may again be again shed in stool
3- Arthritis, vasculitis, and cryoglobulinemia may be seen
4- **Prognosis is excellent** for complete recovery even after multiple relapses (particularly common in children).

Complications

1- Chronic hepatitis:
  - Persistent elevation of liver enzymes > 6 months
  - With HCV, HBV, HDV and rarely HEV

2- HCC:
  - Due to chronic hepatitis (bridging fibrosis and cirrhosis)
  - With HBV and HCV

3- Post hepatitis syndrome
  - Normal enzymes but persistent symptoms
  - Easy fatigue, malaise and pain in right hypochondrium
  - Reassurance and follow up

4- Aplastic anemia
5- Henoch-Schonlein purpura
6- Lichen planus: with HCV
7- Membranous glomerulonephritis: with HBV
8- Membranoproliferative GN: with HCV

Laboratory features

Self limited disease

1- Most prominent biochemical feature: **marked elevation of ALT and AST** (500-5000u/l) with ALT generally > AST

2- **Serum bilirubin level:** uncommonly > 10 mg/dL, except in severe disease, acute liver failure, and cholestatic hepatitis with direct bilirubin > indirect

3- **Serum alkaline phosphatase:** normal or mildly elevated

4- **PT:** normal or increased by 1 - 3 seconds

5- **Serum albumin:** normal or minimally depressed

6- **CBC:** normal or mild leukopenia ± relative lymphocytosis

7- **Urine alysis:**

- Early with marked obstruction → -ve urobilinogen
- Late with relief of obstruction → +ve urobilinogen

8- **Follow up**

- SGOT: decrease with onset of recovery, as its half life is short
- Follow up by SGPT to detect relapse
- Persistent HBsAg for example mean chronic hepatitis or carrier

Acute liver failure

1- Striking coagulopathy with prolonged PT (INR 1.5 or more)

2- Leukocytosis

3- Hyponatremia, and hypokalemia common

4- Hypoglycemia

5- Marked elevations of serum bilirubin and aminotransferase levels, but enzymes may decline toward normal despite disease progression

6- Mild to moderate hypoalbuminemia

Cholestatic disease

1- Serum bilirubin: may > 20 mg/dL

2- Serum aminotransferase: may declining toward normal despite cholestasis

3- Serum alkaline phosphatase: Variable elevation

4- Serum albumin: Normal or nearly normal

5- PT: Prolonged and responsd to vitamin K administration

Relapsing hepatitis

1- After normalization or near-normalization of enzymes and bilirubin levels, both may rise again

2- Infrequently, peak levels may exceed those of the initial bout

Differential diagnosis

1- Drug- and toxin-induced liver disease

2- Ischemic hepatitis

3- Autoimmune hepatitis

4- Alcoholic hepatitis

5- Acute biliary tract obstruction

6- Reactivation of chronic hepatitis B or C

7- Genetic disorders (e.g., Wilson disease)

8- Hepatic vein thrombosis

Serological diagnosis [Patterns]

HAV

1- IgM anti-HAV: is detected during the acute phase and for 3 - 6 months thereafter and rarely for 1year

2- The presence IgG anti-HAV without IgM anti-HAV indicates past infection

HEV

1- IgM and IgG antibodies to HEV (anti-HEV): are detected early by research assays

2- IgA anti-HEV: may be useful for the diagnosis of acute HEV infection in patients who test negative for IgM anti-HEV

3- IgM anti-HEV: may persist for at least 6 weeks after the peak of illness

4- IgG anti-HEV: may remain detectable for 20 months in self limited infection

5- The presence of HEV RNA in stool or serum: is confirmatory but usually unnecessary unless chronic hepatitis E is suspected on follow up

Agent	Acute phase	Convalescence
HAV	- Total anti-HAV positive - IgM anti-HAV positive	- Development of IgG anti-HAV - Disappearance of IgM anti-HAV
HEV	- IgM anti-HEV positive and/or HEV RNA (in stool or serum) - IgG anti-HEV may be present	- Loss of HEV RNA; development of IgG anti-HEV - Loss of IgM anti-HEV
HBV	- HBsAg positive and IgM anti-HBc positive	- Loss of HBsAg; later loss of IgM anti-HBc; development of IgG anti-HBc;

		late development of anti-HBs
HDV	- HDV RNA positive or IgM anti-HDV positive in HBsAg-positive patient - HDV/HBV coinfection: IgM anti-HBc positive - HDV/HBV superinfection: IgG anti-HBc positive	- Loss of HDV RNA; development of IgG anti-HDV or loss of anti-HDV - Above plus usual loss of HBsAg - Above usually without loss of HBsAg
HCV	- Early presence of HCV RNA; presence of or development of anti-HCV	- Loss of HCV RNA (in a minority of patients); anti-HCV persistence for decades

HBV

1-IgM anti-HBc + HBsAg:

- Both are usually present at the onset of symptoms
- IgM anti-HBc is usually preceded by HBsAg
- HBsAg is the first routinely measured serologic marker of HBV infection to appear (before increase of enzymes).
- HBsAg may disappear, usually within several weeks to months after appearance (average: 3-6 months), before the loss of IgM anti-HBc
- If HBsAg persists > 6 months + increased liver enzymes → chronic hepatitis
- If HBsAg persists > 6 months + normal liver enzymes → carrier??
- IgM anti-HBc: is positive in window gap (period in which HBsAg and HBsAB are negative)

2- HBeAg and HBV DNA:

- HBV DNA in serum is the first detectable marker of HBV infection but is not routinely measured
- HBeAg is usually detectable after the appearance of HBsAg (indicate active viral replication).
- Both markers disappear after weeks to months in self-limited infection; corresponding antibodies anti-HBs and anti-HBe persist
- HBeAg: indicates high infectivity in acute or chronic hepatitis

3- **IgG anti-HBc**

  - Replaces IgM anti-HBc in resolving infection
  - Indicates past or continuing infection
  - Not induced by HBV vaccine

4- **Anti-HBs**

  - The last antibody to appear (after 3-4 months from infection) and persists for years
  - Is a neutralizing antibody (IgM → recent infection & IgG → old infection)
  - Indicates recovery and immunity to reinfection (so, no need for vaccine)
  - Elicited by HBV vaccine

5- **HBcAg**

  - Present in hepatocytes (not in blood) and detected only by biopsy

6- **HBeAB**

  - Low infectivity and convalescence

HDV

1- **An HBsAg-positive individual:**

  - Anti-HDV or circulating HDV RNA is detected
  - IgM anti-HDV may be present transiently

2- **HBV/HDV acute coinfection:**

  - HBsAg positivity
  - IgM anti-HBc-positivity
  - Anti-HDV and/or HDV RNA detectable

3- **HDV superinfection of HBV carrier:**

  - HBsAg positivity
  - IgG anti-HBc positivity
  - Anti-HDV and/or HDV RNA detectable

4- **Anti-HDV titers:** decline to undetectable levels with resolution of infection

HCV

1- **Anti-HCV**

- Anti-HCV is detected in approximately 60% of patients during the acute phase of illness; anti-HCV appears weeks to months later in most of the remainder
- < 5% of infected patients doesn't develop anti-HCV (esp. with HIV).
- Anti-HCV persists for prolonged periods following acute infection in both self-limited and chronic HCV infections
- Measured by Elisa or RIBA methods
- Does not indicate immunity

2- **HCV RNA (PCR):**

- The earliest marker of acute HCV infection
- Appears within a few weeks of exposure
- Expensive; not routinely used for diagnosis except when HCV is suspected in an anti- HCV negative individual
- Useful in identifying neonatal infection
- Present in chronic HCV infection

Treatment

Self limited infection

1- **Outpatient care:** unless persistent vomiting or severe anorexia leads to dehydration (I.V. fluids)

2- Maintenance of adequate caloric and fluid intake [**Diet**]:

- No specific dietary recommendations
- Large breakfast possibly the best-tolerated meal
- Prohibition of alcohol during the acute phase

3- **Rest:**

- Avoid Vigorous or prolonged physical activity
- Limitation of daily activities and rest periods determined by severity of fatigue and malaise (usually when serum bilirubin becomes normal)

4- **Drug therapy:**

- All nonessential drugs discontinued
- No specific drug treatment for hepatitis A, E, D

- Peginterferon alfa ± ribavirin: in acute hepatitis C may reduce risk of chronic infection in those who fail to clear HCV RNA by week 12 - 16 after onset
- No role of oral nucleos(t)ides in uncomplicated acute hepatitis B

Acute liver failure (® in brief)

1- **Intravenous N-acetylcysteine:** beneficial if given early after presentation; corticosteroids of no value

2- Treatment of acute liver failure from HBV with **rapidly acting nucleos(t)ides** (tenofovir, entecavir, and lamivudine) may be tried but efficacy uncertain

3- **Goals**
- Maintenance of vital functions
- Continuous monitoring and supportive measures while awaiting spontaneous resolution of infection and restoration of hepatic function
- Early recognition and treatment of life-threatening complications
- Preparation for liver transplantation if recovery appears unlikely

Cholestatic hepatitis

1- Short-term treatment with prednisone or ursodeoxycholic acid: may shortened the course, but no clinical trials of efficacy are available

2- Cholestyramine: for Pruritus

Relapsing hepatitis

1- Management is identical to that of self-limited infection

Prevention

HAV

1- **Preexposure immunoprophylaxis**
- Inactivated HAV vaccine
  - Highly effective (protection 95% - 100%)
  - Highly immunogenic (nearly 100% in healthy subjects)
  - Protective antibodies induced in 15 days after first dose in 85% to 90%
  - Validity: 20 - 50 years, possibly lifelong

    - Side effects: Injection site soreness
  - HAVRIX and VAQTA: doses and schedules
    - Adults ≥ 19 years: two-dose (1440 ELISA U) regimen of HAVRIX, with the second dose at 6 to 12 months after the first
    - Adults ≥ 19 years: two-dose (50 U) regimen of VAQTA with the second dose at 6 to 18 months after the first
    - Children > 12 months of age: half the dose in the 2 regimens
  - Indications for inactivated HAV vaccine
    - All children beginning at age 12 - 23 months
    - Travelers to high-risk areas and residents in high risk areas
    - Laboratory workers handling HAV
    - Food handlers
    - Patients with chronic liver disease

2- Postexposure immunoprophylaxis

  - Inactivated HAV vaccine:
    - Effective as immune globulin if given within 2 weeks of the onset of exposure for individuals between ages 2 and 40 years
    - Validity: longer-lasting than immune globulins
    - The second vaccine dose: should be given 6 to 18 months later
  - Immune globulins:
    - Dose: 0.02 mL/kg body weight, deltoid injection, as early as possible after exposure (within 6 days of exposure)
    - Indications: household and intimate contacts of individuals with acute HAV infection who refuse or cannot have HAV vaccine
    - Validity: short-term protection (3-6 months)

HEV

1- IgG anti-HEV: may be protective

2- HEV vaccine: highly effective in phase 2 clinical trial in endemic areas, and may soon be available

3- Development of high-titer, hyperimmune globulin

HBV

1- Preexposure immunoprophylaxis with HBV vaccine

- Recombinant yeast-derived vaccines
    - Contain HBsAg as the immunogen
    - Highly immunogenic, inducing protective levels of anti-HBs in > 95% of healthy young (< 40 years) recipients after all three doses
    - Protection: 85% - 95%
    - Side effects : transient pain at the injection site in 10% - 25% & short-lived, mild fever in < 3%
    - Validity: 15- 20 years after initial immunization (may lifelong protection)
    - To check vaccine: anti-HBs measured at 7-9 months after the initial dose
    - Boosters: should be given only for immunocompromised individuals if the anti-HBs titer is < 10 mU/mL on annual testing
- HBV vaccine doses and schedules
    - Engerix-B:
      I.M. in deltoid at 0,1,6 months
      Adults > 19 yr: dose of 20 µg; infants and children < 19 years: 10-µg doses; for patients undergoing hemodialysis: 40 µg dose is given at 0, 1, 2, and 6 months
    - Recombivax HB:
      Adults > 19 yr: dose of 10 µg; infants and children < 19 years: 5-µg doses; for patients undergoing hemodialysis: 40 µg dose given at 0, 1, and 6 months

- Indications
    - Universal infant immunization
    - All newborn babies of HBsAg +ve mothers
    - Catch-up vaccination of adolescents through 19 years (if not previously vaccinated) is recommended
    - Targeted high-risk groups
      Household contacts of HBV carriers
      Health care workers

Homosexuals and bisexuals
Injecting drug users
Recipients of high-risk blood products (e.g. hemophilia and chronic hemolytic anemia)
Maintenance hemodialysis patients
Preexisting liver disease (e.g., chronic hepatitis C)

2- Postexposure immunoprophylaxis with HBV vaccine and HBIG (a preparation of immune globulin containing high titers of anti-HBs)

- Indications
  - Susceptible sexual contacts of acutely HBV-infected individuals
    0.04 - 0.07 mL/kg HBIG as early as possible after exposure (within 24hr or at most 7 days)
    First of three HBV vaccine doses given at another site (deltoid) at the same time or within days
    Second and third vaccine doses given 1 and 6 months later
  - Neonates of HBsAg-positive mothers identified during pregnancy
    A dose of 0.5 mL of HBIG given within 12 hr of birth into the anterolateral muscle of the thigh
    HBV vaccine, in doses of 5 - 10 µg, given within 12 hr of birth (at another site in the anterolateral muscle), repeated at 1 and 6 months
- Protective efficacy: > 95%

HDV

1- No vaccine nor immune globulins are available

2- Prevented by prevention of HBV by use of HBV vaccine

HCV

1- No vaccine available: despite neutralizing antibodies have been identified

2- Decrease **risk of transfusion** associated HCV infection:

    - Anti-HCV screening
    - Nucleic acid testing for HCV RNA of blood
    - Improved donor selection

3- **Safe sexual practice:** for contacts of HCV-infected individuals with more than one partner

4- Needle-exchange programs: may reduce the risk in injection drug users

Combined HAV and HBV Vaccine

1- **Twinrix:** containing 20 μg of HBsAg protein (Engerix-B) and more than 720 ELISA U of inactivated hepatitis A virus (Havrix) provides dual protection with three injections spaced at 0, 1, and 6 months

2- For more rapid protection, an **accelerated schedule** with three injections at 0, 7, 21 to 30 days and a booster at 1 year is also available

3- **Indicated for** susceptible individuals at risk of both HAV and HBV infections

4- Approved for **adults only**

Autoimmune hepatitis

Definition

1- **Self-perpetuating hepatic inflammation** of unknown cause characterized by:

    - Interface hepatitis

- Hypergammaglobulinemia
- Liver-associated autoantibodies

2- **Exclusion of other conditions** that have similar features, including:

- Wilson disease
- Chronic viral hepatitis
- Alpha-1 antitrypsin deficiency
- Hereditary hemochromatosis
- Drug induced liver disease (most commonly, minocycline toxicity)
- Celiac disease
- Nonalcoholic Steatohepatitis
- PBC
- PSC

Clinical and laboratory features

1- **Acute severe (fulminant) onset is rare**

- But possible as part of new-onset disease or spontaneous exacerbation of previously unrecognized chronic disease.
- So, duration of 6 months is not required for diagnosis

2- **Easy fatigability** (85%): most common symptom

3- **Hepatomegaly** (78%): in severe or advanced disease

4- **Jaundice** (69%): in severe or advanced disease

5- **Weight loss**: unusual

6- **Intense pruritus**: against diagnosis

7- **Hyperbilirubinemia** in 83%: but serum level usually less than threefold ULN (54%)

8- **Serum alkaline phosphatase level:**

- Frequently increased (81%)
- But usually < twofold ULN (67%)
- Values > fourfold ULN unusual (10%) and suggestive of alternative or variant diagnosis

9- **Polyclonal hypergammaglobulinemia** typical, with predominance of IgG fraction

10- Diverse **nonspecific serologic findings:**

- Common, including antibodies to bacteria (Escherichia coli, Bacteroides, and Salmonella) and viruses (measles, rubella, and cytomegalovirus)

11- Concurrent **extrahepatic immune diseases** frequent (38%):

- Type 1 autoimmune hepatitis
  - Autoimmune thyroiditis (12%)
  - Graves' disease (6%)
  - Ulcerative colitis (6%)
  - Rheumatoid arthritis (1%)
  - Pernicious anemia (1%)
  - Systemic sclerosis (1%)
  - Coombs-positive hemolytic anemia (1%)
  - Idiopathic thrombocytopenic purpura (1%)
  - Leukocytoclastic vasculitis (1%)
  - Nephritis (1%)
  - Erythema nodosum (1%)
  - Fibrosing alveolitis (1%)
- Type 2 autoimmune hepatitis
  - Vitiligo
  - Insulin dependent diabetes mellitus
  - Autoimmune thyroiditis

12- **SMA, ANA, and anti-LKM1** required for the diagnosis: but other autoantibodies possible

Diagnosis

1- **Interface hepatitis** is required for the diagnosis [but lobular (panacinar) hepatitis in conjunction with interface hepatitis is within the histologic spectrum]

- Interface hepatitis
  - Disruption of the limiting plate of the portal tract by mononuclear inflammatory infiltrate that extends into the acinus
- Panacinar hepatitis
  - Mononuclear inflammatory cells line the sinusoidal spaces in association with liver cell degenerative and regenerative changes

2- **Plasma cell infiltration** → characteristic but not specific or essential for the diagnosis

3- **Centrilobular necrosis** → rare and may be an early or acute histologic stage

4- **Prominent cholestatic changes** (bile duct injury, ductopenia) or histologic features suggestive of other disease (fat, granulomas, copper or iron) exclude the diagnosis

5- **Conventional serologic markers** of autoimmune hepatitis:
  - ANA
  - SMA
  - Anti-LKM1

6- **Other nonstandard serologic markers** are:
  - Antibodies to soluble liver antigen (anti-SLA)
  - Antibodies to liver cytosol type 1 (anti-LC1)
  - Atypical perinuclear antineutrophil cytoplasmic antibodies (pANCA); [They support a probable diagnosis of autoimmune hepatitis if conventional markers are absent].

7- **Two scoring systems** are used for the diagnosis of difficult cases:
  - The revised original scoring system of the International Autoimmune Hepatitis Group (IAIHG), which is most useful in patients with few or atypical symptoms
  - The simplified scoring system of the IAIHG, which is most useful in patients with other diseases and concurrent autoimmune features

Basic diagnostic tests of autoimmune hepatitis:

Diagnostic tests	Clinical value

ALT/AST, bilirubin, ALP& γ- globulin levels	- Estimate severity of inflammatory activity - Characterize pattern of liver injury
Albumin, PT/INR	- Estimate impairment of hepatic synthetic function.
ANA, SMA, anti-LKM1, AMA	- Document presence and nature of immune activity.
Serum immunoglobulin levels	- Confirm mainly IgG elevation
Liver tissue examination	- Document that histologic changes support diagnosis - Exclude findings suggestive of other diagnoses
HBsAg, anti-HBc, IgM anti-HAV, and anti-HCV	- Document absence of concurrent viral infection
Ceruloplasmin level	- Exclude Wilson disease
α_{-1} antitrypsin phenotype	- Exclude α_{-1} antitrypsin deficiency
Serum iron, transferrin, iron saturation, & ferritin levels	- Exclude hereditary hemochromatosis

International criteria for the definite or probable diagnosis of AIH:

Diagnostic features	Definite diagnosis	Probable diagnosis
Exclusion of risk factors of other diseases	- Daily alcohol <25 g/day. - No recent hepatotoxic drugs. - Normal α_{-1} AT phenotype. - Normal ceruloplasmin level. - Normal iron and ferritin levels. - No active hepatitis A, B, and/or C infection.	- Daily alcohol <50 g/day. - No recent hepatotoxic drugs. - Heterozygous α_{-1} AT deficiency. - Abnormal copper or ceruloplasmin levels but Wilson's disease is excluded. - Nonspecific iron and/or ferritin abnormalities. - No active hepatitis A, B, and/or C infection
Inflammatory indices	- Serum AST/ALT elevation. - Minimal-mild cholestatic changes	- Serum AST/ALT elevation. - Minimal-mild cholestatic changes
Auto-antibodies	- ANA, SMA, or anti-LKM1 > 1:80 in adults and > 1:20 in children. - No AMA	- ANA, SMA or anti-LKM1 ≥ 1:40 in adults. - Other autoantibodies.
Immunoglobulins	- Globulin, γ-globulin or IgG level >1.5 times normal.	- Hypergammaglobulinemia of any degree

Histologic findings	- Interface hepatitis,moderate to severe. - No biliary lesions, granulomas or prominent changes suggestive of another disease.	- Interface hepatitis, moderate to severe. - No biliary lesions, granulomas or prominent changes suggestive of another disease

Revised original international scoring system for the diagnosis of autoimmune hepatitis

Factor		Score	Factor	Score
Female gender		+2	Alcohol use <25 g/day	+2
Alkaline phosphatase	>3	−2	Alcohol use >60 g/day	−2
AST/ALT ratio	<1.5	+2	HLA DRB1*03 or DRB1*04	+1
γ-globulin or IgG levels	- >2 normal	+3	Concurrent immune disease	+2
	- 1.5–2 normal	+2	Other liver-related autoantibody	+2
	- 1–1.4 normal	+1		
			Interface hepatitis	+3
ANA, SMA, or anti-LKM1	>1:80	+3	Plasmacytic infiltrate	+1
	1:80	+2	Rosettes	+1
	1:40	+1	No characteristic features	−5
	<1:40	0	Biliary changes	−3
Antimitochondrial Antibodies		+4	Other features (fat, granulomas)	−3
Viral markers	+ve	−3	Treatment response complete	+2
	-ve	+3		
			Relapse	+3
Hepatotoxic drugs	Yes	−4		
	No	+1		
Pretreatment score:	- Definite diagnosis	>15	Post-treatment score:	
			- Definite diagnosis	>17
	- Probable diagnosis	10–15	- Probable diagnosis	12–17

Simplified international scoring system for the diagnosis of autoimmune hepatitis

Variable	Result	Points
Autoantibodies		
ANA or SMA	≥1:40	+1
ANA or SMA	≥1:80	+2
anti-LKM1	≥1:40	+2
anti-SLA	Positive	+2
Immunoglobulin level		
Immunoglobulin G	>ULN	+1
	- >1.1 ULN	+2
Morphologic features [Histology]	Compatible Typical	+1 +2
Viral disease markers	No viral markers	+2
Pretreatment aggregate score:		
Definite diagnosis		≥7
Probable diagnosis		6

Treatment

1- Indications of treatment

- Treatment indicated in all patients with active liver inflammation
- Degree of hepatic dysfunction: does not compel therapy in the absence of inflammatory activity
- Laboratory tests of liver inflammation and histologic patterns of liver injury influence urgency of treatment
- Untreated asymptomatic patients with mild disease have poorer 10-year survival than do treated patients with severe disease (67% versus 98%) and warrant therapy

Urgent	**Non-urgent**	**Non-indicated**
Incapacitating symptoms or acute severe (fulminant) onset	Mild or no symptoms	Minimal or no symptoms and AST < 3-fold normal
AST/ALT ≥ 10-fold ULN	AST/ALT < 10-fold ULN and γ-globulin < 2-fold ULN	Portal hepatitis
AST/ALT > 5-fold ULN & and γ-globulin ≥ 2-fold ULN	Interface hepatitis	Inactive cirrhosis
Bridging necrosis	Active cirrhosis	Decompensated inactive cirrhosis with intractable ascites, hepatic encephalopathy, and/or variceal bleeding
Multilobular necrosis	------------	----------

2- **Treatment regimens:**

- **Prednisone alone or a lower dose of prednisone plus azathioprine** is effective in all forms of autoimmune hepatitis
- **The combination regimen** is preferred because of a lower risk of corticosteroid-related side effects (10% versus 44%)
- The combination regimen with azathioprine requires determinations of **leukocyte and platelet counts** at regular intervals (every 1 - 3 months) to monitor for bone marrow toxicity
- **Follow-up assessments** should occur every 6 months during treatment, or sooner if symptoms of liver failure or drug intolerance are noted
- No findings at presentation preclude a satisfactory **response to treatment**; ascites and encephalopathy identify patients with a poor prognosis but do not contraindicate therapy
- **Patients with multilobular necrosis** on histologic examination who fail to resolve at least one laboratory parameter or improve pretreatment hyperbilirubinemia during a 2-week treatment period have high immediate mortality; they should be evaluated for liver transplantation if features of decompensation are present
- **In Europe**, prednisolone in an equivalent dose is preferred over prednisone

Standard treatment regimens

Regimens	**Drugs**		**Relative contraindications**
	Prednisone (daily dose)	Azathioprine (daily dose)	
Prednisone and azathioprine	30 mg × 1 wk 20 mg × 1 wk 15 mg × 2 wks 10 mg maintenance till end point.	50 mg maintenance until end point	- Severe cytopenia - Thiopurine methyltransferase deficiency - Pregnancy - Active neoplasm
Prednisone only	60 mg × 1 wk. 40 mg × 1 wk. 30 mg × 2 wks. 20 mg maintenance	Non	- Obesity - Osteopenia - Emotional instability - Brittle DM - Labile hypertension - Acne

3-Drugs related side effects [if no time cancel]

- Corticosteroid-induced complications
  - Cosmetic changes: facial rounding, facial hirsutism, dorsal hump formation, striae, weight gain, acne and alopecia
  - Metabolic: diabetes, obesity, hyperlipidemia and HTN
  - Skeletal: osteopenia, avascular necrosis and vertebral compression esp. Postmenopausal women esp. in re-treatment
  - Psychiatric: emotional instability and psychosis
  - Somatic: cataract formation, pancreatitis, opportunistic infection and malignant disease
- Corticosteroid-induced cosmetic changes are most common (80% after 2 years of therapy).
- Severe corticosteroid-induced side effects are infrequent and usually require at least18 months of treatment with prednisone (20 mg daily).
- Severe corticosteroid-induced side effects warrant premature discontinuation of treatment in 13% (mainly because of intolerable obesity, cosmetic changes, or osteoporosis).

- Regular weight-bearing exercise, calcium (1 to 1.5 g/day), and vitamin D3 (400 U/week) comprise an appropriate adjuvant program for preservation of bone density in all adult patients; alendronate (70 mg once each week) is indicated for progressive osteopenia
- Azathioprine-induced complications include:
  - Cytopenia: most common side effect of azathioprine (46%)
  - Cholestatic hepatotoxicity
  - Nausea, emesis
  - Rash, opportunistic infection
  - Pancreatitis
  - Severe myelosuppression in up to 10% treated with 50 mg daily
  - Side effects are frequently reversible with dose reduction or termination of therapy
- Complications of treatment (weight gain, cushingoid appearance, fluid retention, cytopenia, worsening liver tests) may be difficult to distinguish from complications of liver disease (cytopenia is most commonly associated with cirrhosis).
- Thiopurine methyltransferase activity should be determined in patients with pretreatment cytopenia or cytopenia developing during azathioprine treatment

4- Standard treatment end points

- Liver biopsy examination is necessary before drug withdrawal to establish remission; as significant residual inflammatory activity occurs in 55% of patients with normal laboratory study results

Feature	Definition	Occurrence	Action	Outcome
Remission	- Ideal endpoint: no symptoms, normal liver testes, normal liver tissue. - Satisfactory end point: no symptoms, AST/ALT ≤ 2-fold ULN, normal other tests, no interface	77% within 2 yr (age related)	- Gradual drug withdrawal over 6 weeks.	- Relapse in 50 % within 6 mo or sustained remission

	hepatitis.			
Ttt Failure	- Increase AST/ALT and/or bilirubin > 67% and/or worse histologic activity.	9%	- Prednisone 60 mg/day or - prednisone 30 mg & azathioprine 150 mg/day.	- Gradual dose reduction to maintenance L - Clinical and laboratory improvement in 70% - Histologic improvement in 20 % - Indefinite therapy
Incomplete response	- Improvement but insufficient to satisfy remission criteria after 3 yr.	13%	- Long-term treatment (low-dose prednisone or indefinite azathioprine).	- Indefinite therapy
Drug toxicity	- Intolerable side effects (e.g. progressive cytopenia or vertebral compression).	13%	- Dose reduction or - Elimination of offending agent, continue with tolerated agent.	- Indefinite therapy with single tolerated drug or low-dose offending agent

5-Withdrawal schedule after remission

- Corticosteroid withdrawal after an ideal or satisfactory end point is gradual over a 6-week period after the treatment end point

Wks after remission	Combination regimen		Single-drug regimen
	Prednisone (mg/day)	Azathioprine (mg/day)	Prednisone (mg/day)
1	7.5	50	15
2	7.5	50	10
3	5	50	5
4	5	25	5
5	2.5	25	2.5
6	2.5	25	2.5
Thereafter	None	None	None

6- Follow up

- ■ AST/ALT, bilirubin, and γ-globulin levels
  - During treatment withdrawal: every 3 weeks
  - After stoppage of treatment: every 3 weeks for 3 months
  - Then: every 6 months for 1 year after remission
  - Then: every 1 year if remission is sustained

7- Liver transplantation

- Effective in decompensated patients in whom corticosteroid therapy has failed
- 5-year patient survival and graft survival range from 83% - 92%; actuarial 10-year survival is 75%.
- Disease recurs in 12% - 46%, usually 1 - 8 years after transplantation (median, 2 years) and mainly in recipients who are inadequately immunosuppressed
- Recurrent and de novo AIH must be excluded in all patients with graft dysfunction after liver transplantation

8- Long-term treatment regimens after multiple relapses

Features	Low-dose prednisone	Azathioprine only
Indication	- Clinical and laboratory remission after previous relapse and repeat standard therapy	- Clinical and laboratory remission after previous relapse and repeat standard therapy
Schedule	- Reduce prednisone dose by 2.5 mg/mo until lowest level to prevent symptoms and maintain AST <3-fold ULN (no interface hepatitis) - Gradual azathioprine withdrawal	- Increase azathioprine to 2 mg/kg daily - Gradual prednisone withdrawal
Outcome	- Improved steroid-related side effects, 85% - New side effects, 0% - Liver-related mortality, 9%	- Weight loss, 43% -Hypertension improved, 13% - Liver-related mortality, 1%
Limitations	- Possible long-term steroid-related complication	- Corticosteroid withdrawal arthralgias, 53% - Lethargy, 10% - Malignancy, 7% - Myelosuppression, 6% - Uncertain teratogenicity

Prognosis

1- Overall 10- year survival : is 93%

2- HCC: occurs in 0.5% of patients followed long term

Overlap syndrome [variants of AIH]

Overlap syndrome with PBC

1- **Definition:**

- Features of autoimmune hepatitis, antimitochondrial antibodies (AMA), and histologic findings of bile duct injury or loss

2- **Diagnosis:**

- Most (88%) patients with AMA titers up to 1:160
- Seropositivity for antibodies to M2 autoantigens rare (8%)
- AMA reactivity possibly false because of confusion with anti-LKM1 by IIF

3- **Treatment:**

- If autoimmune features predominant and alkaline phosphatase level less than twice the upper limit of normal (ULN)
    - Empiric treatment (3 - 6 months) with prednisone alone (20 mg daily)
    - Or prednisone (10 mg daily) plus azathioprine (50 mg daily) is effective
- If PBC features predominant, alkaline phosphatase level more than twice the ULN, and/or florid duct lesions on histologic examination
    - Prednisone (20 mg daily) combined with ursodeoxycholic acid (13 - 15 mg/kg daily)

Overlap syndrome with PSC

1- **Definition:**

- Features of autoimmune hepatitis, cholestatic biochemical changes, histologic evidence of cholestasis including bile duct injury or loss, and abnormal bile ducts by ERC or MRC

2- Diagnosis:

- Cholangiography required for diagnosis if inflammatory bowel disease present
- Histologic features of small duct PSC:
    - Bile duct injury
    - Portal edema
    - And/or ductopenia
    - And normal cholangiogram
- Clues to diagnosis:
    - Inflammatory bowel disease
    - Suboptimal response to corticosteroid therapy
    - And/or rising serum alkaline phosphatase level
- Biliary changes by MRC in 8% of adults with classic AIH, but similar frequency by MRC in non-autoimmune liver diseases and may incorrectly implicate PSC
- Children may present with AIH and abnormal cholangiograms in the absence of inflammatory bowel disease (“autoimmune sclerosing cholangitis”)

3- Treatment:

- Empirical therapy with prednisone (20 mg daily) and ursodeoxycholic acid (13 - 15 mg/kg daily) justified
- Children with autoimmune sclerosing cholangitis typically respond to corticosteroid therapy but have shorter transplant-free survival than patients with normal bile ducts

AIH and chronic viral hepatitis

1- **Definition:**

- Concurrence of active viral hepatitis, high-titer autoantibodies, and histologic features of interface hepatitis with or without portal plasma cell infiltration

2- **Diagnosis:**

- Definite or probable autoimmune hepatitis by diagnostic scoring systems defining autoimmune predominant disease with background coincidental viremia
- **Nondiagnostic autoimmune features** by diagnostic scoring systems with active viremia defining viral predominant disease with coincidental autoimmune findings
- **Immune manifestations** common in chronic viral hepatitis, including SMA in 11%, ANA in 28%, diverse autoantibodies in 62%, and concurrent immune disease in 23%
    - SMA and ANA titers typically low in chronic viral hepatitis (up to 1:80 in 89%, 1:160 or higher in 11%; 1:320 or higher rarely)
    - Concurrent positivity for SMA and ANA in only 4% of patients with chronic viral hepatitis
    - Median serum titers of SMA and ANA in classical autoimmune hepatitis of 1:160 and 1:320, respectively; 60% with concurrent SMA and ANA; and only 6% with isolated titers up to 1:80
- **Liver tissue evaluation** essential in discriminating predominantly autoimmune from predominantly viral hepatitis
    - Moderate to severe portal plasma cell infiltration (66% versus 21%), acinar (lobular) inflammation (47% versus 16%), and interface hepatitis (23% versus 0%) more common in autoimmune-predominant disease

- Portal lymphoid aggregates (49% versus 10%), steatosis (72% versus 19%), and bile duct damage or loss (91% versus 20%) more frequent in viral-predominant (chronic hepatitis C) disease

3- **Treatment:**

- Treatment administered according to the prevailing condition:
    - Corticosteroids for autoimmune-predominant disease
    - Peginterferon and ribavirin for viral-predominant disease (chronic hepatitis C)
- Treatment results assessed at 3 months, and therapy changed if response poor

AIH with cholestatic syndrome

1- **Definition:**

- Heterogeneous syndrome with composite features of autoimmune hepatitis and AMAnegative PBC or small duct PSC

2- **Diagnosis:**

- ANA and/or SMA typically present in women with cholestatic biochemical changes, normal cholangiogram, absent AMA, and/or histologic findings of bile duct injury or loss
- Possible resemblance to mainly PBC or autoimmune hepatitis

3- **Treatment:**

- Variable response to empirical therapy with corticosteroids, ursodeoxycholic acid, or both
- Possible therapy-induced improvements in clinical and laboratory findings but not in histologic changes

Cryptogenic chronic hepatitis

1- **Definition:**

- Satisfies international criteria for diagnosis of autoimmune hepatitis but lacks conventional autoantibodies (SMA, ANA, anti-LKM1)
- Possibly representing a form that has escaped detection by conventional serologic markers

2- Diagnosis:

- Similarities in age, female predominance, frequency of concurrent immune diseases, histologic features, occurrence of HLA B8, DRB1*03 and A1-B8-DRB1*03, and laboratory findings to classic autoimmune hepatitis
- Conventional autoantibodies possibly appearing late, or possible presence of nonstandard autoantibodies (atypical pANCA, anti-SLA)
- Must be distinguished from inactive cryptogenic cirrhosis and liver disease associated with celiac disease (i.e., negative for IgA antibodies to tissue transglutaminase or endomysium)

3- Treatment:

- Should be considered “autoantibody-negative autoimmune hepatitis” and treated with conventional corticosteroid regimens (responsive as in autoantibody-positive patients)

Drug induced hepatitis

Background

1- **Incidence**:

- The overall incidence is about 14 per 100,000 population annually
- Medications cause about 50 % of cases of fulminant hepatic failure

2- **Risk factors for drug-induced liver injury**

- Extremes of age
- Females and pregnancy
- Obesity and malnutrition
- Alcoholism
- Pre-existing liver diseases
- Previous drug-induced liver injury
- Polypharmacy and long-acting drugs

3- **Drug metabolism:**

- ■ Orally administered drugs are lipid-soluble which allows them to be absorbed
- ■ Drug-metabolizing systems convert the parent drugs into water soluble compounds which allow excretion into bile or urine
- ■ The metabolizing systems are divided into:
- Phase I reactions:
    - Involve the cytochrome P-450 (CYP) family of enzymes
    - Include addition of polar groups by oxidation, reduction or hydrolysis

- Influenced by age, other drugs and toxins [drugs and conditions that affect activity of cytochrome P-450 (CYP)]:

Inhibit CYP activity	**Induce CYP activity**
○ Increasing age ○ Clarithromycin. ○ Erythromycin. ○ Fluconazole. ○ Itraconazole. ○ Ketoconazole. ○ Metronidazole. ○ Ritonavir. ○ Amiodarone. ○ Cimetidine. ○ Grape fruit. ○ Quinidine.	○ Chronic alcohol use. ○ Carbamazepine. ○ Phenobarbital. ○ Phenytoin. ○ Rifampin. ○ Glucocorticoids. ○ Quinine. ○ Griseofulvin.

- Phase II reactions:
  - Involve conjugation of glucuronide, sulfate, acetate, glycine or glutathione to a polar group
  - Occasionally, phase II reactions may affect the parent compounds directly i.e. without previous exposure to phase I reactions
  - Influenced by age, dietary factors and nutritional status

4- Mechanisms of drug-induced hepatitis:

- Intrinsic drug reactions:
  - Dose-related
  - Toxicity occurs within a few days i.e. short latency
  - Classic example is acetaminophen toxicity
- Idiosyncratic drug reactions:
  - Unrelated to dose
  - Variable latency (1 wk up to 1 year)
  - Classified as:

Hypersensitivity	**Metabolic-idiosyncratic**
- Immune-related response	- Related to indirect metabolite of the offending drug
- Characterized by rash, fever and eosinophilia	- No clinical manifestations of hypersensitivity are noted
- Short latency period 1-4 wks	- Variable latency (1 wk-1yr)
- Example includes phenytoin, amoxicillin-clavulanate, sulfonamides and halothane	- Example includes INH toxicity

Clinical manifestations

1- **Hepatitis pattern:**

- Asymptomatic elevation of liver enzymes
- Fatigue, right upper quadrant pain, jaundice or acute liver failure
- Most commonly accompanied by acute liver failure, defined as coagulopathy (INR ≥1.5) and hepatic encephalopathy occurring <26 weeks after onset of illness in a patient without pre-existing cirrhosis. This usually has a grave prognosis in absence of liver transplantation
- Jaundice is a good predictor of mortality in drug-induced hepatitis. Hy's Law: A consistent serum bilirubin ≥ 3 × ULN in the absence of biliary obstruction or Gilbert's syndrome is associated with a mortality of approximately 10% (range, 5–50%).

2- **Cholestatic pattern:**

- Presentation can mimic biliary obstruction or the course can be more indolent with jaundice and pruritus
- Mortality appears to be less than with the hepatitis pattern (1–7.8%) and death is usually not liver-related, though chronic cholestatic injury can result in ductopenia and, rarely, cirrhosis

3- **Mixed pattern:**

- Combination of acute hepatitis and cholestasis
- This pattern of liver injury probably has the lowest mortality

Pathological manifestations

Pattern of liver injury	Examples

Hepatitis	
a. immune mediated (allergic).	Allopurinol, diclofenac, methyldopa, phenytoin, propythiouracil.
b. Non-immune mediated (non-allergic).	Paracetamol, methothrexate, acarbose, troglitazone, amiodarone, pyrazinamide, rifampicin, isoniazide, ketoconazole, sodium valproate.
Cholestatic	
a. immune mediated (allergic).	ACE inhibitors, amoxicillin/clavulanate, erythromycin, cotrimoxazole, sulfonamides, Phenobarbital, sulindac, carbamazepine.
b. Non-immune mediated (non-allergic).	Anabolic steroids, oral contraceptives, azathioprine, cyclosporine.
Fibrosis/cirrhosis	Methotrexate.
Granulomas (allergic)	Allopurinol, amoxicillin/clavulanate, sulfonamides, phenytoin, carbamazepine.
Micro-vesicular steatosis	Sodium valproate.
Neoplasms	
a. Adenoma.	Anabolic steroids, oral contracetives.
b. Angiosarcoma.	Anabolic steroids, Arsenic.
c. Cholangiocarcinoma.	Anabolic steroids.
d. Hepatocellular carcinoma.	Anabolic steroids, danazole.
Non-alcoholic steatohepatitis	Amiodarone.
Phospholipidosis	Amiodarone.
Vascular lesions	
a. Budd-Chiari.	Oral contraceptives.
b. Peliosis hepatis.	Oral contraceptives, anabolic steroids, azathioprine.
c. Perisinusoidal fibrosis.	Methotrexate, vitamin A.
d. Veno-occlusive disease.	Cyclophosphamide.

Diagnosis

1- Clinically

- Drug-induced liver injury should be suspected when liver injury occurs after the initiation of treatment with a certain agent or after an increase in the dose

- Resolution of the injury after withdrawal of the suspected drug is supportive of diagnosis
- Exclusion of other causes of liver disease is required before the diagnosis of drug-induced liver injury

2- **Laboratory:** there is no specific test for drug-induced liver injury

- Exclusion of other liver diseases:
    - Hemolytic anemia → CBC
    - Viral hepatitis → HAV IgM, HBsAg (and HDV IgM), HCV Ab, HEV IgM
    - Auto-immune hepatitis → ANA, γ-globulin
    - Primary biliary cirrhosis → anti-mitochondrial Ab
    - Primary sclerosing cholangitis → ASMA
- Assessment of liver affection:
    - Bilirubin
    - Transaminases (ALT, AST): To diagnose hepatocellular disease and assess progression
    - ALP: To diagnose cholestasis and infiltrative disease
    - Albumin: To assess severity of liver injury
    - PT, PC and INR after vit K: To assess severity of liver injury
- Determination of pattern of liver injury:
    - Hepatotoxicity due to drugs can be categorized by the biochemical pattern of liver injury according to the following equation:

R = ALT (measured in multiples of upper limit of normal "ULN") / ALP (measured in multiples of upper limit of normal)
- $R > 5$ → hepatocellular injury - $R < 2$ → cholestatic injury - $2 < R < 5$ → mixed injury

3- **Imaging:** to exclude other causes of liver pathology

- Ultrasonography: is effective to evaluate gall bladder, bile ducts, and hepatic tumors
- CT scanning: detect focal hepatic lesions 1 cm or larger and some diffuse conditions
- MRI: used to detect cysts, hemangiomas, and primary and secondary tumors

Management

1- **Withdrawal** of the suspected agent

2- **Liver transplantation** for fulminant hepatic failure may be lifesaving

3- **Glucocorticoids** for drug hepatotoxicity with allergic features, **silibinin** for hepatotoxic mushroom poisoning, and **ursodeoxycholic acid** for cholestatic drug hepatotoxicity have never been shown to be effective and are **not recommended**

Exampels of drug induced liver injury

Acetaminophen

1- **Toxicity:**

- Acetaminophen overdose is the most common cause of drug-induced liver injury and fulminant hepatic failure
- The amount ingested as a single dose required to produces hepatic injury is 10–20 g, while in alcoholics it can be as low as 5–10 g.
- In overdoses, intake exceeds 15 g in 80 % of serious or fatal cases.
- Up to 2 g daily appears safe, even in patients with cirrhosis

2- **Factors that increase acetaminophen:**

- Alcoholism
- Malnutrition or fasting may play a role by reducing glutathione stores

- The use of concurrent medications that induce cytochromes P-450 **(see above)**.

3- **Mechanism of acetaminophen toxicity:**

- Acetaminophen is normally metabolized by conjugation to glucuronide and sulfate, with a relatively small amount being metabolized by cytochrome P-450 to form oxidative metabolites
- When large quantities are ingested, the glucuronide and sulfate conjugation pathways become saturated and more metabolism via cytochrome P-450 occurs
- Increased formation of one of the oxidative metabolites, *N*-acetyl-*p*-benzoquinoneimine (NAPQI), leads to depletion of intracellular glutathione, allowing it (NAPQI) to bind to certain cell macromolecules disrupting mitochondrial function
- Depletion of glutathione by starvation or alcohol ingestion may further augment NAPQI toxicity

4- **Clinical phases of massive ingestion:**

- Acute gastrointestinal symptoms (nausea, vomiting, anorexia) occur ½ – 24 hrs post-ingestion
- Cessation of gastrointestinal symptoms is followed by a period of well-being for about 48 h.
- Right-sided abdominal pain occurs with oliguria and the appearance of abnormal liver chemistry tests and a prolonged prothrombin time
- Hepatic necrosis occurs 3–5 days after ingestion. Serum aminotransferase levels may exceed 20 000 U/L
- The recovery phase occurs 5–10 days after ingestion without residual histologic damage

5- **Prognosis:**

- Fulminant hepatic failure develops in up to 30 % of patients
- Renal failure from proximal and distal renal tubular damage occurs in up to 20 %.

6- **Management of overdose:**

- Goals of management:
  - Reduce further absorption of ingested acetaminophen
  - Replete hepatic glutathione via ***N*-acetylcysteine (**NAC).
- Therapy:
  - Gastric wash and oral administration of activated charcoal or cholestyramine to prevent absorption of residual drug
  - Avoid any other potentially hepatotoxic medications

N-acetylcysteine (NAC)		
Dose	**Mechanism of action**	**Side effects**
-140 mg/kg orally followed by 70 mg/kg orally every 4 hrs for an additional 17 doses - It should be started even if the patient presents several days post-ingestion	- Enhances glutathione synthesis - Provides a glutathione substitute to inactivate NAPQI - May provide a substrate to enhance the nontoxic sulfation pathway - May act as an antioxidant to modify secondary effects of inflammation - May act on microcirculatory blood flow and improve tissue oxygenation	- It may induce nausea and vomiting, so careful monitoring of the administration is vital and sometimes nasogastric tube placement may be necessary

Antimicrobial drugs

1- **Antibiotics:**

- **Amoxicillin-clavulanic acid:**
  - The most frequently reported antibiotic that causes hepatotoxicity
  - It can cause a predominant cholestatic injury.
  - Liver injury usually manifests within 2 weeks of starting the drug, but delayed onset up to 8 weeks following cessation of therapy is seen
  - The probability of persistent liver damage and death or need for LT is about 10%

    - Progressive vanishing bile duct syndrome following discontinuation of therapy has also been seen

- **The natural penicillins (penicillin G):**
    - Display little evidence of hepatotoxicity, but the semisynthetic penicillins are responsible for a wide range of liver injury.
    - Recognized risk factors are older age and treatment for 14 days or longer.
- **First-generation cephalosporins**:
    - Rarely have hepatotoxic potential.
    - Ceftriaxone has been implicated in the formation of biliary sludge

- **Erythromycin**:
    - The estolate, ethylsuccinate, propionate, and stearate esters of erythromycin have all been implicated in the production of cholestatic jaundice
- **Sulfonamides** (including sulfasalazine used in the treatment of inflammatory bowel disease):
    - Most frequently cause a necroinflammatory liver injury
    - But may also provoke a cholestatic, mixed, or granulomatous hepatitis
- **Trimethoprim-sulfamethoxazole**:
    - Causes a predominantly cholestatic injury that may be severe and last for many months.
    - Patients with HIV infection are particularly susceptible to trimethoprim-sulfamethoxazole hepatotoxicity
- **Fluoroquinolones:**
    - Less frequent than other antibiotics to cause DILI

2- Anti-tuberculous:

- **Isoniazid** (INH):

  - Toxicity is rare in patients under age 20, but the frequency is greater than 2 % in patients over age 50
  - Women and alcoholics are at greatest risk
  - Patients positive for hepatitis B surface antigen, have an 8–10 fold increased risk of toxicity
  - Continuing INH after clinical liver injury occurs may result in fulminant hepatitis with a high mortality
  - The mechanism of hepatotoxicity is via cytochrome P-450 transformation of the parent compound into a toxic acetyl radical

- **Rifampin:**
  - The hepatotoxic potential is low when rifampin is taken alone.
  - However, when rifampin is taken with INH, there is greater hepatotoxicity than with either drug alone.
  - This combination may result in clinical hepatitis in 5–8 % of patients. Fulminant hepatitis may occur within the first week of treatment

- **Pyrazinamide:**
  - Hepatotoxicity with high-dose (40–50 mg/kg) pyrazinamide alone is more common than with standard-dose INH alone
  - It appears that pyrazinamide-based anti-tuberculosis regimens result in more severe liver injury and an increased risk of acute liver failure

- **Streptomycin and ethambutol:**
  - Very rarely hepatotoxic

3- Antiretroviral Agents:

- Drugs against HIV cause hepatotoxicity in 3-18 % of patients
- Drug-induced liver injury may be more common in patients with viral hepatitis, especially hepatitis C
- Protease inhibitor, **ritonavir** (especially at high dose) has the highest risk of liver toxicity, with an incidence of 3-9 %.

- The newer protease inhibitor, **tipranavir** has been associated with severe hepatotoxicity, especially when used in combination with ritonavir and particularly in patients with hepatitis B or C

4- **Interferon**:

- May provoke elevation of liver enzymes in patients with chronic hepatitis B or C or in patients with concurrent autoimmune hepatitis
- Pegylated INF may induce de novo autoimmune hepatitis and an accelerated form of chronic ductopenic rejection after liver transplantation

5- **Antifungals:**

- **Ketoconazole:**
  - It can cause inconsequential liver biochemical abnormalities with a necroinflammatory pattern in as many as 3–10 % of patients taking the drug
  - The mechanism is thought to be idiosyncratic, and toxicity affects mainly middle-aged women.
  - Several instances of fulminant hepatic failure have been reported
- **Fluconazole:**
  - It has also been associated with modest serum aminotransferase elevations
  - There have been reports of associated fatal hepatic necrosis

NSAIDs

- ■ Despite the overall extremely low incidence of NSAID-induced hepatotoxicity, widespread use of these agents makes them an important class of potentially hepatotoxic drugs.
- ■ Nearly all NSAIDs have been implicated in causing liver injury, ranging from mild to severe
- ■ Most NSAIDs produce injury in an unpredictable fashion via an idiosyncratic mechanism that is often hepatocellular in nature

1- **Diclofenac:**

- Hepatotoxicity is most likely to occur in older women with osteoarthritis
- Most cases occur within 3 months of the start of therapy, with a mixed hepatocellular/cholestatic picture
- The US Food and Drug Administration (FDA) recommends that liver enzyme tests be checked within 2 months of starting treatment with diclofenac
- Severe hepatitis and even acute liver failure can occur, but the prognosis is good if the drug is stopped quickly

2- Sulindac:

- Most cases occur in older women and present frequently with features of hypersensitivity
- Sulindac is accompanied by a higher incidence of hepatotoxicity than most other NSAIDs; it has been listed in 25 % of the reported cases of liver injury associated with NSAIDs

3- Aspirin:

- Liver enzyme abnormalities due to aspirin toxicity are almost always mild, asymptomatic, and reversible
- In 30 % of cases serum aminotransferase levels are less than 100 U/L and in 45 % between 300 and 500 U/L. Serum bilirubin and alkaline phosphatase levels are frequently normal
- Liver injury is dose dependent and related to serum salicylate levels. 90 % of toxic cases have a level greater than 15 mg/dL, which is easily achieved with the large doses used in the treatment of some rheumatologic disorders

Lipid lowering agents

1- Hepatotoxicity is an infrequent side-effect, usually dose-dependent, and causes **asymptomatic serum aminotransferase elevations**, typically within the first year of therapy

2. Serious toxicity from **statin agents** is rare. The risk of fulminant liver failure associated with lovastatin, the first of the statins to be approved for treatment of hypercholesterolemia, is about 1 in 1 million patient-treatment years, a value that is similar to the rate of idiopathic fulminant liver failure.
3. **Monitoring of liver tests** at baseline, within 12 weeks, and every 6 months is recommended

Hormonal agents

1. **Oral contraceptive**
    - Cause frequent, **reversible liver biochemical test abnormalities**; some patients may develop overt cholestatic jaundice
    - **The molecular basis of injury** may be due to an alteration of the basolateral membrane of the hepatocyte with a resulting decrease in bile flow
    - **Other conditions** associated with use of oral contraceptives include:
        - Cholestasis of pregnancy
        - Hepatic adenoma (risk increases with duration of use and is higher in women over age 35).
        - Budd–Chiari syndrome (may be related to thrombogenic effect of the estrogenic component).
        - Possibly focal nodular hyperplasia
2. **Anabolic and androgenic steroids**
    - Peliosis hepatis
    - Cholestatic jaundice
    - Hepatic adenoma (possible association)
    - HCC
3. **Flutamide**
    - Oral androgen used in treatment of metastatic prostate cancer
    - Associated with idiosyncratically mediated modest elevation of aminotransferases and rarely massive hepatocellular necrosis

Cardiovascular drugs

1- **Amiodarone:**

   - Up to five-fold serum aminotransferase elevations are seen in 40 % of patients taking long-term amiodarone
   - The drug should be discontinued when aminotransferase levels are twice normal, and a liver biopsy should be considered

2- **Angiotensin-converting enzyme (ACE) inhibitors:**

   - Captopril, enalapril, and lisinopril have each been implicated in causing hepatic injury
   - Captopril typically produces cholestatic, lisinopril hepatocellular, and enalapril acute mixed hepatocellular and cholestatic injury

3- **Angiotensin II receptor inhibitors:**

   - Drug injury has been observed with irbesartan (cholestatic hepatitis), candesartan (transient rise in serum aminotransferases), and losartan (hepatocellular injury).

4- **Calcium channel blockers:**

   - Necroinflammatory injury has been reported with verapamil
   - Mixed hepatocellular and cholestatic injury with nifedipine.
   - Granulomatous hepatitis and hepatocellular injury have been reported with diltiazem

5- **Alpha-methyldopa (aldomet)**

   - Can cause transient aminotransferase elevations to chronic hepatitis and even ALF
   - Chronic hepatitis can be histologically indistinguishable from autoimmune hepatitis

6- **Antiarrhysthmic drugs**

   - Quinidine and procainamide can cause granulomatous hepatitis

Glycemic agents

1- **Metformin**

   - Impaired hepatic function is a risk factor for the development of lactic acidosis in patients receiving metformin

2- **Thiazolidinedione**

- Removed from the market because of the numerous reports of DILI, sometimes fatal

Neurologic and antipsychotic agents

1- **Chlorpromazine**

- The incidence of drug-induced **jaundice** may be as high as 1% - 5%, and **asymptomatic liver chemistry** test abnormalities have been reported in up to 25% of patients
- **Onset of jaundice** typically occurs within 1 - 4 weeks of initiation of treatment. Recovery usually occurs within 2 to 8 weeks with discontinuation of the drug, although symptoms resembling those of primary biliary cirrhosis can persist
- **Bilirubin levels** may be as high as 5 to 15 mg/dL, and alkaline phosphatase may be up to 10 times the ULN, with moderate elevations of aminotransferase levels
- **Pronounced hypercholesterolemia** is common. Histologically, centrilobular cholestasis is seen with periportal inflammation, usually including eosinophils

2- **Carbamazepine (Tegretol):**

- This is structurally similar to tricyclic antidepressants.
- It is reported to produce mild to moderate liver chemistry test elevations in up to 20% of patients within the first 6 - 8 weeks of therapy

3- **Phenytoin**

- Asymptomatic aminotransferase elevations are common, with clinically significant liver injury in 0.1% of patients
- Most patients with **clinical hepatotoxicity** have hypersensitivity-type symptoms, including eosinophilia, fever, leukocytosis, lymphadenopathy, and rash (pseudolymphoma). Cholestatic liver injury and ALF have also been reported

4- **Valproic acid (Depakene)**

- This is a common cause of asymptomatic aminotransferase elevations, which are usually mild, reversible, and dose dependent
- **Fatal valproate hepatotoxicity** is not dose dependent, occurs in young patients who are often receiving other anticonvulsants, and appears to be idiosyncratic. Liver biopsy shows microvesicular steatosis accompanied by centrilobular necrosis

5- **Phenothiazines, other neuroleptics** (e.g., haloperidol), and less frequently benzodiazepines and barbiturates (e.g., phenobarbital):

- Can cause cholestatic liver injury probably secondary to delayed hypersensitivity.

6- **Tricyclic antidepressants (e.g., amitriptyline)**

- Can produce hepatocellular injury

Chemotherapeutic agents

1- **Alkylating agents** :

- Are uncommonly associated with DILI.
- **Cyclophosphamide and ifosfamide** do require dose reduction in the setting of liver dysfunction.
- Cyclophosphamide is infrequently hepatotoxic; alkylating agents such as melphalan, chlorambucil, nitrogen mustards, and busulfan do not depend on hepatic metabolism

2- **Antitumor antibiotics**:

- Such as **doxorubicin and daunorubicin** can cause hepatocellular injury and steatosis, so dose reductions are recommended in patients with liver disease

3- **Antimetabolites:**

- Such as **thiopurines, cytarabine, and 5-fluorouracil** depend on hepatic metabolism, and thus dose reductions are often necessary in patients with liver dysfunction

Immunosuppressive medications

1- **Methotrexate:**

- Hepatotoxicity has been recognized for several decades in patients being treated for psoriasis.
- The spectrum includes hepatic steatosis, fibrosis, and cirrhosis
- Cumulative dose of methotrexate appears to be the greatest risk factor for the development of cirrhosis; a total dose of 1.5 g is associated with significant liver disease
- American College of Rheumatology guidelines for monitoring liver toxicity of methotrexate in rheumatoid arthritis:

- Assess baseline serum aminotransferases, alkaline phosphatase, albumin, bilirubin, hepatitis B and C serologies, complete blood count and serum creatinine
- Pretreatment liver biopsy recommended only for patients with a history of prior excessive alcohol consumption, persistently elevated baseline serum aminotransferase levels, or chronic hepatitis B or C
- Serum aminotransferase and albumin levels should be checked at 4–8-week intervals, with liver biopsy reserved for patients with persistent liver test abnormalities, defined as an elevation in AST in 5 of 9 determinations within a 12-month period of time, or 6 of 12 determinations if monthly tests are performed, or an abnormal decrease in serum albumin
- Routine surveillance liver biopsies are not recommended
- Patients should understand the possible risk factors for the development of significant hepatotoxicity, including alcohol consumption, cumulative dose, and increasing age
- With persistent liver enzyme abnormalities, the dose of methotrexate should be decreased, followed by temporary discontinuation if liver enzymes remain abnormal. Liver biopsy should be considered before the drug is restarted

2- Thiopurines (azathioprine/6-mercaptopurine/6-thioguanine)

- Associated with a wide range of hepatotoxic reactions including nodular regenerative hyperplasia, veno-occlusive disease, and, most commonly, cholestasis and asymptomatic elevation of aminotransferase levels
- Hepatotoxicity seems to correspond to **high thioguanine methyltransferase (TPMT) activity**. High TPMT enzyme activity

preferentially shunts thioguanine metabolism toward an increase in the production of the metabolite 6-methylmercaptopurine ribonucleotide (6-MMP); this can be detected on a commercially available **assay**

- Concurrent use of allopurinol affects thioguanine metabolism

3- Biologic therapy

- As a class, tumor necrosis factor (TNF) antagonists are known to cause **elevated aminotransferase** levels and need to be used cautiously in patients with liver disease
- Agents such as etanercept (Enbrel), adalimumab (Humira), and infliximab (Remicade) have also been associated with triggering **autoimmune hepatitis**, and numerous cases of ALF have been reported
- Screening patients for chronic hepatitis B before starting biologic therapy or any chemotherapeutic regimen is mandatory, to prevent reactivation of hepatitis B by using an oral antiviral agent

CHRONIC HEPATITIS

Chronic HBV infection

Definition of chronic hepatitis

1- Condition characterized by persistent liver inflammation for **≥ 6 months** after initial exposure or diagnosis of liver disease

2- Complications include: cirrhosis, portal HTN, hepatic failure, and HCC

Clinical features and natural history

1- Asymptomatic or

2- **Nonspecific complaints** (fatigue, right upper quadrant pain) or

3- **Complications of cirrhosis**

4- **Extrahepatic manifestations:** (in 20%)

- Arthralgias
- Polyarteritis nodosa
- Glomerulonephritis
- Mixed essential cryoglobulinemia, and a few other rare syndromes

5- **The risk of chronicity depends on** the age and immune function when a person is infected; chronic infection occurs in

- 90% of infants infected during the first year of life
- 30% - 50% of children infected between 1-4 years old
- Approximately 5% of healthy adults
- > 50% of immune compromised adults

6- **Approximately 25% of adults** who become chronically infected during childhood will die at some point in their lifetime of HBV-related liver cancer or cirrhosis.

7- **The prevalence of hepatitis B e antigen** (HBeAg) declines with age, with spontaneous loss of HBeAg in 7% to 20% of patients per year

8- **Spontaneous loss of hepatitis B surface antigen** (HBsAg) occurs infrequently (0.5% to 1% per year); with most patients developing anti-HBs

9- **Factors associated with progression** of chronic hepatitis B include

- Older age (longer duration of infection)
- HBV genotype C
- Alcohol abuse
- High levels of HBV DNA
- Concurrent infection with other viruses ([HIV], HCV, HDV)
- Environmental factors (smoking, aflatoxin)
- Obesity
- Diabetes mellitus

10- **The natural history** of chronic hepatitis B is outlined

11- **Phases of HBV chronic infection**

	immune tolerance Phase	immune active HBeAg +ve CHB	inactive carrier	Reactivation HBeAg -ve CHB	HBsAg -ve
HBsAg	+	+	+	+	-ve
Anti-HBs	-	-	-	-	+ve/-ve
Anti-HBc	+	+	+	+	+ve
HBeAg	+	+	-	-	
Anti-HBe	-	-	+	+	
ALT	Normal	Elevated	Normal	Elevated	Normal
Liver biopsy	Normal or minimal inflammation	Active inflammation	Normal or minimal inflammation	Active inflammation	Normal or minimal inflammation
HBV-DNA level	High $2x10^{8-11}$	Low $2x10^{4-10}$	Very low < 2000	Fluctuating $2x10^{3-8}$	Undetectable in blood & low in liver biopsy
Therapy candidate	No	Yes	No	Yes	No

Serologic and virologic tests

1-The diagnosis mainly by detection of **HBsAg**

2-If HBsAg is positive → further laboratory testing to assess disease status and need for treatment is indicated:

- Quantitative HBV DNA by PCR: fluctuating levels need serial monitoring
- ALT levels: can fluctuate; test ALT every 3 - 6 months if ALT is persistently normal and more often when elevated
- HBeAg and anti-HBe:
  - Define the type of chronic hepatitis B (i.e., HBeAg positive or HBeAg negative)
  - Define the end point of therapy (i.e., loss of HBeAg in HBeAg-positive patients).
- Tests of liver disease severity:
  - Platelet count
  - Total bilirubin

    - Serum albumin
    - INR
- Liver biopsy:
    - Optional
    - Determine the histologic grade (necroinflammation) and stage of disease (fibrosis)
    - Identify coexistent liver diseases such as steatohepatitis, iron overload, or autoimmune hepatitis
    - Characteristic histologic findings of chronic hepatitis B: include ground-glass hepatocytes in which the cytoplasm is stained pink with hematoxylin-eosin in response to massive production of HBsAg; HBcAg can be demonstrated in the hepatocyte nuclei, within the cytoplasm and on the cell membrane
- Noninvasive tests of fibrosis: such as serum fibrosis markers and transient elastography (need more studies).

Treatment

1- Goals of treatment

- Prevention of long-term complications (cirrhosis, HCC) and mortality by durable suppression of serum HBV DNA
- 1ry treatment end point: sustained decrease in serum HBV DNA level to low or undetectable (< 10 - 15 IU/mL)
- 2ry treatment end points:
    - Decreased or normalized ALT
    - Improved liver histology
    - Induced HBeAg loss or seroconversion
    - Induced HBsAg loss or seroconversion
    - Prevention of secondary spread of infection

2-Treatment criteria for chronic hepatitis B

- No consistent correlation between clinical and laboratory parameters and liver histology

- So, guidelines recommend liver biopsies only in select patients based on age, HBV DNA levels, and HBeAg status

Guideline*	**HBeAg-Positive**		**HBeAg-Negative**	
	HBV DNA, IU/mL	ALT	HBV DNA, IU/mL	ALT
EASL 2009	>2,000	>ULN†	>2,000	>ULN†
APASL 2008	≥20,000	>2 × ULN†	≥2,000	>2 × ULN†
AASLD 2009	>20,000	>2 × ULN‡ or abnormal biopsy	≥20,000§	≥2 × ULN‡ or abnormal biopsy

* No universal agreement for level of elevation of ALT and HBV DNA that warrants consideration of treatment.

† Normal for laboratory.

‡30 U/L for men and 19 U/L for women.

§ In patients > 40 years old, 2000 IU/mL should be considered as the minimum cutoff for treatment.

3- Treatment candidates and indications for HBV treatment

Evidence of benefit: treatment indicated	**Treatment not indicated**
- Decompensated cirrhotic patients - HBV DNA–positive cirrhotic patient - Fulminant liver failure - HBsAg-positive patient who is going to be immunosuppressed - Chronic hepatitis B with elevated ALT levels and HBV DNA >2000 IU/Ml	- Immune tolerance phase - Inactive chronic carrier - Acute hepatitis B

4-Drugs

- Current first line therapies
  - Peginterferon alfa-2a (exceptions: pregnancy, chemotherapy prophylaxis, decompensated cirrhosis)
  - Entecavir
  - Tenofovir
- The first decision is selection of either a nucleos(t)ide analogue or peginterferon.
- Predictors of HBeAg response are the same for peginterferon and nucleos(t)ide analogues
- Specific drugs

	Peginterferon	**Nucleos(t)ide analogues**
Indications	Young, noncirrhotic patients with low HBV DNA levels, high ALT levels, and a favorable genotype (better in genotype A > B > C > D).	Despite their high antiviral potency (greater than that of interferon), these drugs are not able to eradicate HBV, but they can maintain the sustained suppression of replication
Advantages	- Finite treatment - Absence of resistance - Seroconversion in up to 32% of HBeAg-positive patients at 48 weeks of treatment - Clearance of HBsAg in 6% of patients	- Potent - Negligible adverse effects - Oral administration - Safe and effective at all ages - Suitable for cirrhotic and HIV-coinfected patients
Drawbacks	- Many adverse effects - Subcutaneous injections - Frequent contraindications	- Lower rates of HBeAg and HBsAg seroconversion - Prolonged treatment required, leading to an increasing risk of antiviral drug resistance
Schedule of ttt	180 µg/week subcutaneously for 48 weeks	See below

	Nucleotide analogue		**Nucleoside analogue**		
	Adefovir dipivoxil	**Tenofovir**	**Lamivudine**	**Entecavir**	**Telbivudine**
Dose	10 mg daily	300 mg daily	100 mg daily	0.5 to 1 mg daily	600 mg/daily
Side effects	Potentially nephrotoxic	- Fanconi syndrome (rare) - Decrease in bone density - Less nephrotoxic than adefovir	The most common mutation leading to lamivudine resistance is a specific point mutation in the conserved YMDD motif of the HBV polymerase		Very infrequently can cause - Myopathy - Peripheral neuropathy
Effect	Less potent, but with higher genetic	Potent, with high genetic	Potent, with low genetic	Potent antiviral activity with high	Potency similar to that of

	barrier and lower rate of resistance	barrier and low rates of resistance	barrier and high rate of resistance	genetic barrier and low rate of resistance	entecavir, but with a resistance rate of 22% the second year of treatment; telbivudine-resistant mutations cross-resistant with lamivudine

5- **Duration of HBV therapy with nucleos(t)ide analogues**

- HBeAg positive: treat until HBeAg seroconversion, and stop after consolidation period 6 - 12 months after HBeAg seroconversion
- HBeAg negative: treat indefinitely because relapse is common after cessation of therapy

6- **Resistance to antiviral drugs**

- Diagnosis of resistance
  - Viral rebound by at least 1.0 log10 compared with nadir; confirmed with repeat HBV DNA testing
  - Exclusion of non-HBV–related causes of failure (i.e., poor adherence)
  - Confirmation of genotypic resistance with HBV mutant detection, if available
  - Genotypic resistance; detection of HBV polymerase mutation(s) associated with resistance
  - Phenotypic resistance; decreased in vitro susceptibility to an antiviral agent in compliant patients
- Monitoring for drug resistance
  - Repeated ALT and serum HBV DNA measurements
  - Use of sensitive HBV DNA assay and the same assay over time
  - Frequency of assessments adapted according to disease severity (mild liver disease: at least 6 monthly; advanced disease or cirrhosis: 3 monthly)

- Management of resistance to HBV antiviral drugs

Resistance	Rescue Therapy
Lamivudine	- Add adefovir or tenofovir* - Switch to entecavir (increased risk of entecavir resistance) - Switch to emtricitabine/tenofovir†
Adefovir	- Add lamivudine or telbivudine - Switch to or add entecavir (if no previous resistance to lamivudine) - Switch to emtricitabine/tenofovir†
Entecavir	- Add or switch to adefovir or tenofovir* - Switch to emtricitabine/tenofovir†
Telbivudine	- Add adefovir or tenofovir* - Switch to entecavir (increased risk of entecavir resistance) - Switch to emtricitabine/tenofovir†

*Tenofovir preferred, if available.
†Truvada.

7- Algorithm for management of patients receiving oral therapy for chronic HB

8- Liver transplantation

- Treatment of choice in end-stage chronic liver disease
- Without prophylactic measures: HBV recurrence is universal, and post-transplant survival is reduced
- Perioperative and postoperative HBIG: reduces recurrence and improves survival
- Nucleos(t)ide analogues: given before and after transplantation as well as for post-transplantation recurrence
- The prophylactic strategy most commonly accepted: is the combination of HBIG with an oral antiviral (preferably one with high barrier to residstance); this regimen has reduced the risk of recurrent hepatitis B in the graft to < 10%.

Prevention

See prevention of acute viral hepatitis [write main items only ®]

EASL guidelines 2012 for treatment of chronic HBV

Pretherapeutic assessment of liver disease

1- **Assessment of liver disease severity:**
   - Biochemical (i.e. ALT/AST, GGT/ALP, PC/PT, bilirubin, albumin/globulin, CBC)
     - Usually ALT levels are higher than AST, however when disease progress to cirrhosis the ration may be reversed
     - After cirrhosis has developed, a progressive decline in serum albumin concentrations &/or increase of (gamma)globulins (i.e. inverted A/G ration) and prolonged prothrombin time, often accompanied by declining platelet counts, are characteristically observed
   - U/S: can detect cirrhotic pattern

2- **HBV-DNA measurement:** is essential for
   - Diagnosis & decision to treated of follow-up
   - Follow-up: using real-time PCR is strongly recommended due to their sensitivity, specificity, accuracy

3- **Assessment of other causes of liver disease:**
   - Co-infection with HDV, HCV or HIV should be looked for
   - Co-morbidities: including alcoholic, autoimmune, metabolic liver disease with steatosis or steatohepatitis should be assessed

4- **Liver biopsy:**
   - Significance:
     - Recommended for determining the degree of necroinflammation & fibrosis
     - Useful for evaluating other possible causes of liver disease such as fatty liver disease
   - Not indicated:
     - Not required in patients with clinical evidence of cirrhosis

- In patients in whom treatment is indicated irrespective of the grade of activity or the stage of fibrosis

Goals of therapy

1- Improve quality of life

2- Improve survival by preventing progression of the disease to cirrhosis, decompensated cirrhosis, end-stage liver disease, HCC and death

Endpoints of therapy

1- The ideal end point is **HBsAg loss** which infrequently achievable with the currently available anti-HBV agents

2- The realistic end point is the induction of sustained or maintained virological **remission**

Definitions of response

1- Biochemical response:

- Normalization of ALT levels.
- Since ALT activity often fluctuates over time, a minimum follow-up of at least 1 year post-treatment with ALT measurements at least every 3 months is required to confirm sustained off-treatment biochemical response

2- Serological response: for

- HBeAg:
  - Is applied only for HBeAg +ve patients
  - Is defined as HBeAg loss & seroconversion to anti-HBe
- HBsAg:
  - Is applied to all CHB patients
  - Is defined as HBsAg loss and development of anti-HBs

3- Virological response:

- **On INF-therapy:**
  - Primary non-response has not been well established

- Virological response is defined as an HBV-DNA level of < 2000 IU/ml. It is usually evaluated at 6 months & at the end of therapy as well as at 6 and 12 months after the end of therapy
- Sustained off-treatment virological response is defined as HBV-DNA levels < 2000 IU/ml for at least 12 months after the end of therapy

- **On NA-therapy:**
  - Primary non-response is defined as < 1 $\log_{10}$ IU/ml decrease in HBV-DNA level from baseline at 3 months of therapy
  - Partial virological response is defined as a decrease in HBV-DNA of > 1 $\log_{10}$ IU/ml but detectable HBV DNA after at least 6 months of therapy in compliant patients
  - Virological response is defined as undetectable HBV-DNA by a sensitive PCR assay. It is usually evaluated every 3–6 months during therapy
  - Virological breakthrough is defined as a confirmed increase in HBV-DNA level of > 1 $\log_{10}$ IU/ml compared to the nadir (lowest value) HBV-DNA level on therapy; it may precede a biochemical breakthrough, characterized by an increase in ALT levels. The main causes of virological breakthrough on NA therapy are poor adherence to therapy &/or development of resistance
  - Sustained off-treatment virological response:
    © Since, NA(s) discontinuation is not common practice to date, it may be defined similarly to the definition used for IFN therapy (i.e. HBV-DNA values < 2000 IU/ml for at least 12 months after treatment discontinuation)

4- Histological response:

- Is defined as decrease in necroinflammatory activity (by ≥ 2 points in HAI or Ishak's system) without worsening in fibrosis compared to pre-treatment histological findings

5- **Complete response:**

  - Is defined as sustained off-treatment virological response together with loss of HBsAg

Indications for treatment

1- **The indications for treatment** are generally the same for both HBeAg-positive and HBeAg-negative CHB. This is based mainly on the combination of three criteria:

  - Serum HBV DNA levels > 2000 IU/ml
  - Serum ALT levels > upper limit of normal (ULN)
  - Severity of liver disease (by biopsy or non-invasive measures), showing moderate or severe active necroinflammation &/or at least moderate fibrosis using standardized scoring system

2- **The need for liver biopsy and treatment** should be considered separately in the following subgroups of patients:

  - Immunotolerant patients: (without any evidence of liver disease, persistently normal ALT)
    - They do not require immediate liver biopsy or therapy
    - Follow-up (ALT every 3 months & HBV-DNA every 6–12 months) is mandatory
    - Consider liver biopsy or even therapy if:

      © < 30 years of age
      © Cirrhosis or any evidence of liver disease
      © Family history of HCC
  - HBeAg-negative patients: (without any evidence of liver disease, persistently normal ALT)
    - They do not require immediate liver biopsy or therapy
    - Follow-up with (ALT every 3 months & HBV-DNA every 6–12 months for 3 years) is mandatory, after 3 years, they should be followed for life like all inactive chronic HBV carriers (i.e. they

are advised to perform liver biopsy in case of ALT elevations even if HBV-DNA is < 2000 IU/ml).

    - Evaluation of the severity of fibrosis by a non-invasive method, such as Fibroscan, might be useful in such cases

- Patients with obviously active CHB: (i.e. ALT > 2 times ULN & HBV-DNA > 20,000 IU/ml)
    - HBeAg +ve & HBeAg -ve patients should start treatment even without a liver biopsy
    - Liver biopsy, in such patients may provide additional useful information, but it does not usually change the decision for treatment
    - A non-invasive method for assessment of fibrosis and most importantly to confirm or rule out cirrhosis is extremely useful in patients who start treatment without liver biopsy
- Patients with compensated cirrhosis and detectable HBV-DNA must be considered for treatment even if ALT levels are normal
- Patients with decompensated cirrhosis and detectable HBV-DNA require urgent antiviral treatment with NA

Predictors of response

For INF-base treatment:

1- Pretreatment factors:

- In HBeAg +ve patients: predictors of seroconversion are
    - Low viral load (HBV-DNA < 2 × 10^8 IU/ml)
    - High serum ALT (> 2–5 times ULN)
    - High activity scores on liver biopsy
    - HBV genotypes A and B

- In HBeAg –ve patients:
    - No strong pre-treatment predictors of virological response

2- During treatment:

- In HBeAg +ve:
    - HBV-DNA decrease to < 20,000 IU/ml at 12 weeks
    - HBsAg decrease to < 1500 IU/ml at 12 weeks
    - Immunologically-induced ALT flares followed by a HBV DNA decrease
    - HBeAg levels at week 24 may also predict anti-HBe seroconversion
- In HBeAg –ve:
    - HBV-DNA decrease to < 20,000 IU/ml at 12 weeks
    - HBsAg decrease to < 1500 IU/ml at 12 weeks

N.B. A combination of no HBsAg decline and < 2 $\log_{10}$ IU/ml decline of HBV-DNA seems to be a predictor of non-response in European HBeAg-negative patients

For NA-based treatment:

1- Pretreatment factors:

- In HBeAg +ve patients: predictors of seroconversion are
    - Low viral load (HBV-DNA $< 2 \times 10^8$ IU/ml).
    - High serum ALT (> 2–5 times ULN).
    - High activity scores on liver biopsy

Unlike INF-base treatment, HBV genotypes don't influence the virological response to any NA

- In HBeAg –ve patients:

- No predictors: no strong pre-treatment predictors

2- During treatment:

- Undetectable HBV-DNA (at 24 weeks for lamivudine or telbivudine & at 48 weeks for adefovir), in both HBeAg +ve & HBeAg –ve
- HBsAg decrease

Treatment stratigies

1- Treatment of finite duration with PEG-INF or a NA:

- INF-based treatment:
    - A 48-week course of PEG-IFN is mainly recommended for HBeAg-positive patients, it can also be used for HBeAg-negative patients
    - The combinations of PEG-IFN with lamivudine or telbivudine are not recommended due to:

      © No more advantages in combination with lamivudine
      © A high risk of severe polyneuropathy with telbivudine
- NA-based treatment:
    - Finite-duration treatment with a NA is achievable for HBeAg +ve patients, however, treatment duration is unpredictable as it depends on the timing of seroconversion
    - The most potent agents with the highest barrier to resistance should be used
    - Once seroconversion occurs, treatment should be prolonged for an additional 12 months, persistence seroconversion can be expected in 40–80% of these patients

2- Long-term treatment with NA:

- Indicated for:
    - HBeAg +ve patients who do not develop seroconversion
    - HBeAg -ve patients (not expected to achieve a sustained off-treatment virological response)
    - Patients with cirrhosis (irrespective of HBeAg status or seroconversion on treatment).
- Drugs:
    - The most potent drugs with the optimal resistance profile, i.e. tenofovir or entecavir, should be used as first-line monotherapies
    - Treatment with either tenofovir or entecavir monotherapy for ≥ 3 years achieves maintained virological remission in the vast majority of patients

Treatment failure

1. **Primary non-response:**
   - Primary non-response is rarely observed with entecavir or tenofovir, telbivudine or lamivudine
   - In patients with primary non-response to any NA, it is important to check for compliance
   - Primary non-response seems to be more frequent with adefovir (approximately 10–20%) than with other NAs because of suboptimal antiviral efficacy
   - In NA(s) naive patients with primary non-response to adefovir, a rapid switch to tenofovir or entecavir is recommended
2. **Partial virological response:**
   - Partial virological response may be encountered with all available NAs
   - It is always important to check for compliance
   - In patients receiving lamivudine or telbivudine (drugs with a low genetic barrier to resistance) with a partial virological response at week 24 or in patients receiving adefovir (moderately potent drug that engenders relatively late emergence of resistance) with a partial response at week 48, change to a more potent drug (entecavir or tenofovir), preferentially without cross-resistance, is recommended
3. **Virological breakthrough:**
   - Virological breakthrough in compliant patients is related to the development of HBV drug resistance
   - The rates of resistance at 5 years in NA naive patients are < 1.5% and 0% for entecavir and tenofovir, respectively, thus, virological breakthroughs in NA naive patients receiving entecavir or tenofovir are usually due to poor drug compliance
   - In case of:
     - **Lamivudine resistance:** switch to tenofovir (add adefovir if tenofovir is not available).

- **Telbivudine resistance:** switch to tenofovir (add adefovir if tenofovir is not available).
- **Entecavir resistance:** switch to or add tenofovir (add adefovir if tenofovir is not available).
- **Adefovir resistance:**

© If NA-naive patient before adefovir, switch to entecavir which is preferred in such patients with high viraemia

© If lamivudine-resistant patient before adefover, switch to tenofovir and add a nucleoside analogue

- **Tenofovir resistance:** (however it hasn't been detected up to date)

© An addition of entecavir, telbivudine, lamivudine or emtricitabine (adding entecavir may be the preferred option for patients with prior lamivudine resistance)

© A switch to entecavir if the patient hasn't been previously treated with lamivudine

Monitoring treatment with stopping endpoint

1- **Finite therapy with PEG-IFN:**

- Periodic monitoring: patients should be tested every
    - Month; for CBC, ALT
    - Three months for TSH
- Safety monitoring: patients should be tested for safety
    - HBeAg +ve patients: should be tested for (HBeAg, anti-HBe Ab & HBV-DNA)

      © At 6 & 12 months of treatment

      © After 6 & 12 months of treatment
    - HBeAg –ve patients: should be tested for (HBV-DNA level)

      © At 6 & 12 months of treatment

      © After 6 & 12 months of treatment

2- **Finite therapy with NA in HBeAg +ve patients:** patients should be tested

- During treatment: every 6 months for HBeAg, anti-HBe Ab & HBV-DNA level
- After treatment (i.e. after seroconversion): every 12 months for HBsAg

3- Long-term therapy with NA:

- HBV-DNA:
    - At 3 months of treatment to check response
    - Every 3-6 months (frequency of monitoring may be decreased once treatment efficacy is confirmed).
- Serum creatinine:
    - Before treatment: to assess kidney functions
    - During treatment: to monitor kidney functions as NAs are cleared by kidneys

Treatment of specific conditions

Treatment of patients with severe liver disease

1- Patients with compensated cirrhosis:

- Drug preference:
    - Monotherapies with tenofovir or entecavir are preferred because of their potency and minimal risk of resistance
    - Lamivudine should not be used in such patients
- Dose: 0.5 mg once daily of entecavir
- Duration:
    - Long-term treatment is recommended
    - After at least 12 months of consolidation therapy, treatment might be stopped:

© **In HBeAg +ve patients if:**
Confirmed anti-HBe seroconversion Or
HBsAg loss and anti-HBs seroconversion

© **In HBeAg-negative patients if:**
Confirmed HBsAg loss and anti-HBs seroconversion

- Follow-up:
    - Careful monitoring: for HBV-DNA levels every 3 months at least during the first year of therapy and until HBV-DNA undetectability is significant
    - Surveillance for HCC is mandatory despite virological remission under NA(s), since there is still a risk of developing HCC

2- Patients with decompensated cirrhosis:

- Drug preference:
    - Monotherapies with tenofovir or entecavir are preferred because of their potency and minimal risk of resistance
    - IFN is contraindicated in this setting as it may enhance decompensation
- Dose: 1 mg once daily of entecavir
- Duration:
    - Long-term treatment is recommended
    - Patients with decompensated cirrhosis may show slow clinical improvement over a period of 3–6 months under NA(s), then transplantation may be avoided
- Follow-up:
    - Monitoring of HBV-DNA levels
    - Surveillance for HCC is mandatory despite virological remission under NA(s), since there is still a risk of developing HCC

Prevention of recurrence after transplantation

1- Drug preference:

- Entecavir prophylaxis without HBIG was shown to be safe and effective in preventing HBV recurrence
- Lamivudine &/or adefovir in combination with hepatitis B immunoglobulin (HBIG) have reduced the risk of graft infection to < 10%.

2- **Duration:**

  - Long-term treatment is recommended, to achieve the lowest possible level of HBV-DNA before liver transplantation

3- **Dose**: 0.5-1 mg once daily of entecavir

4- **Follow-up:**

  - Monitoring of HBV-DNA levels
  - Kidney functions should be closely monitored due to concomitant use of calcineurin inhibitors which are also nephrotoxic

Treatment of HIV coinfected patients

1- **Drug preference:**

  - Tenofovir combined with emtricitabine or lamivudine plus a third agent active against HIV are indicated (simultaneous treatment of both HIV & HBV).
  - The risk of developing cirrhosis is negligible in HBV/HIV co-infected patients on long term tenofovir combined with emtricitabine or lamivudine therapy

2- **Duration:**

  - Long-term treatment is recommended

3- **Follow-up:**

  - Monitoring of HBV-DNA levels as HIV treatment may cause flare of hepatitis B
  - Surveillance for HCC

Treatment of HDV coinfected patients

1- **Drug preference:**

  - PEG-IFN is the only drug effective against HDV
  - NAs might be considered in some patients who have active HBV replication

2- **Duration:**

- > 1 year of therapy, as there may be some benefit from treatment prolongation

3- **Follow-up:**
  - Monitoring of HBV-DNA levels as treatment may cause flare of hepatitis B
  - Surveillance for HCC

Treatment of HCV coinfected patients

1- **Drug preference:**
  - PEG-IFN + Ribavirin are effective against HCV
  - NAs may be indicated in case of HBV reactivation

2- **Duration:**
  - Long-term duration (i.e. 48-week course of PEG-IFN).

3- **Follow-up:**
  - Monitoring of HBV-DNA levels as HCV treatment may cause flare of hepatitis B
  - Surveillance for HCC due to accelerated progression

Treatment of acute hepatitis B

1- **Drug preference:**
  - > 95% of adults with acute HBV infection will recover spontaneously
  - Patients with fulminant or severe hepatitis may be benefited from NA (entecavir or tenofovir should be used), they should be evaluated for liver transplantation

2- **Duration:**
  - The duration is not established.
  - However, continuation of antiviral therapy is recommended for:
    - At least 3 months after seroconversion to anti-HBs Or
    - At least 12 months after anti-HBe seroconversion without HBsAg loss

3- **Follow-up:**

- Monitoring of HBV-DNA level as it may flare up
- Liver functions (e.g. ALT/ASL, PT/INR), for fear of acute liver failure

Treatment of HBV in pregnancy

1- During child-bearing period:

- Family planning:
    - Should be always discussed with women of childbearing age before initiating HBV therapy
- In a woman of childbearing age without advanced fibrosis who plans a pregnancy in the near future:
    - It may be prudent to delay therapy until the child is born
- In a woman of childbearing age with advanced fibrosis or cirrhosis who agrees for a ''planned pregnancy'' in the future:
    - PEG-IFN therapy may be tried as it is given for a finite duration.
    - If PEG-IFN is not possible or has failed, treatment with a NA has to be initiated and maintained even during a future pregnancy

2- During pregnancy:

- PEG-IFN:
    - Contraindicated (i.e. If female patients become unexpectedly pregnant during anti-HBV therapy, PEG-IFN must be stopped, replaced by NAs).
- Lamivudine, adefovir and entecavir:
    - Are listed by the FDA as pregnancy category C drugs
- Telbivudine and tenofovir:
    - Are listed as category B drugs

- There is a considerable body of safety data from the Antiretroviral Pregnancy Registry in pregnant HIV-positive women who have received tenofovir and/or lamivudine or emtricitabine, **tenofovir** should be preferred, because it has better resistance profile and more extensive safety data in pregnant HBV positive women

- If a pregnant woman remains untreated or anti-HBV therapy is discontinued during pregnancy or early after delivery for any reason:
    - Close monitoring of the patient is necessary, as there is a risk of hepatic flares, especially after delivery

3- **During Perinatal period:**

- Breast feeding ca not be considered a contraindication in HBsAg +ve mothers
- Tenofovir concentrations in breast milk have been reported, but its oral bioavailability is limited and thus infants are exposed to only small concentrations

4- **Protection of babies born for HBsAg +ve mothers:**

- Regimen:
    - Combination of passive and active immunization with hepatitis B immunoglobulin (HBIg) and HBV vaccination is recommended
- Prevention of transmissition:
    - Lamivudine and recently telbivudine therapy during the last trimester of pregnancy in pregnant HBsAg +ve women have been shown to be safe and to reduce the risk of intra-uterine and Perinatal transmission of HBV if given in addition to passive (HBIG) and active vaccination HBV vaccine).

Pre-emptive therapy before immunosuppressive or chemotherapy

1- **The risk:** Patients receiving chemo or immuno suppressive therapy are at high-risk of reactivation of HBV if they are HBV-seropositive

2- **Screening**: All patients intended to receive chemo or immunotherapy should be screened for HBsAg & anti-HBc Ab

3- **Indications**: HBV seronegative patients are highly recommended to receive HBV vaccine before receiving chemo or immuno suppressive therapy, higher vaccine doses may be required in such patients

4- **Pre-emptive NA administration** (before chemotherapy & for 12 months after cessation of chemotherapy), should be give for:

   © HBsAg +ve

   © HBsAg –ve with anti-HBc Ab positive & detectable serum HBV-DNA

5- **Excluded patients:** Patients with HBsAg –ve with anti-HBc Ab +ve & undetectable serum HBV-DNA, should be carefully monitored by serum HBV-DNA levels for fear of HBV-DNA reactivation & treatment is promptly initiated if flare-up occurs

6- **The frequency of monitoring** can range from 1–3 months depending on the type of immunosuppressive therapy and comorbidities

7- **Renal dysfunction:** PEG-IFN or NAs can be used for chronic HBV patients with renal dysfunction provided adjustment of the dose, particularly NAs that should be used with caution in patients with renal impairment

8- **Renal transplantation:** PEG-IFN should be avoided in renal transplant patients because of the risk of rejection

Occult HBV infection

Definition

1- Long- lasting persistence of **viral genomes** in the liver tissue (detected by liver biopsy) of individuals negative for HBsAg

2- It may be **explained by**:-

- Persistence of covalently closed circular DNA (cccDNA) in the nucleus of hepatocytes
- Integration of HBV genome in the host genome (that might favor oncogenesis).

Detection of occult HBV infection

1- **Analysis of liver DNA extracts** is the most correct methodological approach for occult HBV detection

Prevalence

1- Occult HBV is detectable in about **$^1/_3$ of HCV-infected** patients who are HBsAg -ve

2- A high prevalence has been reported, with 45% in **intravenous drug addicts**

Clinical importance

1- **Carriers** of occult infection may be a source of HBV transmission through:

- Blood transfusion (occult HBV is the major cause of transfusionally transmitted HBV).
- Organ donation

2- **Reactivation** of occult HBV infection: patients prone to reactivation include

- Patients with
    - Hematological malignancies
    - HIV infection
- Patients underwent
    - Bone marrow transplantation
    - Liver transplantation
    - Kidney transplantation
    - Chemotherapy
    - Treatment with anti-CD20 (Rituximab)
    - Treatment with anti-CD52 (Alemtuzumab)
    - Treatment with anti-TNF (Infliximab)

3- **Occult HBV infection and chronic liver disease:** *occult HBV infection may*

- Favor or accelerate the progression of chronic liver disease in HCV infected individuals
- Exert negative influence on chronic HCV by reduction of response to IFN therapy. However, no reliable studies evaluating whether occult HBV infection may interfere with the response to PEG-IFN plus Ribavirin
- Accelerate progression of liver fibrosis and cirrhosis development in patients with cryptogenic liver disease

4- Occult HBV infection and HCC:

- There is evidence indicates that occult HBV infection is a risk factor for HCC development
- The occult HBV infection appears to exert a pro-oncogenic role in HCV infected patients as well as in alcoholics and patients with cryptogenic liver disease

Management

1- Patients with occult HBV (HBsAg –ve, with detectable HBV-DNA in the liver) and non-detectable HBV-DNA in the serum **don't require immediate therapy**

2- **Careful follow up** by (ALT & HBV-DNA levels) for early detection of reactivation, then treatment is promptly initiated accordingly. (®)

Chronic HCV infection

Pathogenesis [3 mechanisms of HCV related liver injury]

1- Direct cytopathic damage

2- Immune-directed hepatocyte destruction

3- Viral-induced autoimmunity (destruction by sensitized T cells).

Clinical features and natural history

1- Asymptomatic: in most patients

2- If symptoms present:

- The most common symptom is fatigue
- Other symptoms include:
  - Musculoskeletal pain
  - Pruritus
  - Sicca syndrome
  - Depression
  - Anorexia
  - Abdominal discomfort
  - Difficulty with concentration
  - Reduction in quality of life
- The intensity of symptoms is not related to the severity of liver disease

3- Once cirrhosis is established: patients are predisposed to complications of portal hypertension

4- **Jaundice:** is rare until hepatic decompensation occurs

5- **Extrahepatic manifestations:**

  - Up to 40% to 74% of patients develop at least one extrahepatic manifestation during the course of their disease
  - Rheumatologic and cutaneous manifestations are the most common

6- **ALT levels:**

  - Persistent or intermittent elevation in Most patients
  - Normal in 1/3 of cases

7- **Natural history**

  - Disease progression is typically silent
  - Only a few patients have severe outcomes during the first 2 decades of infection; at least 20 - 30 years of infection are required to develop clinically significant disease
  - Once cirrhosis develops, actuarial survival is 83% - 91% at 5 years and 79% after 10 years in the absence of clinical decompensation
  - Survival decreases to 50% at 5 years among those who develop clinical decompensation; the cumulative probability of developing an episode of decompensation is only 4% - 5% at 1 year, and it increases to 30% at 10 years.
  - The risk of developing HCC is 1% - 4% per year once cirrhosis is established
  - Factors associated with progression of chronic hepatitis C include:
    - Male gender
    - Infection after age 40 years
    - Use of alcohol > 50 g/day
    - Immunosuppression
    - Elevated ALT levels
    - Significant necroinflammation and fibrosis
    - Insulin resistance with obesity or DM

Serologic and molecular tests and liver biopsy

1- **Serologic assays:** Anti-HCV ab

- Indicates exposure but does not confirm active infection, because anti-HCV persists indefinitely after spontaneous or therapeutic resolution
- Has sensitivity of 97% - 100%; and positive predictive value of 50% - 95%
- False negative results are more likely in immunosuppressed patients, HIV-positive patients, or patients with chronic renal failure undergoing dialysis

2- Molecular assays:

- Used to confirm active infection
- 2 viral replication markers commonly used: are the presence of viral RNA and core antigen in peripheral blood
- HCV RNA testing should be performed in:
    - All patients with +ve anti-HCV assay
    - Patients for whom antiviral treatment is being considered (quantitative assay)
    - Patients with unexplained liver disease whose anti-HCV result is negative if they are immunocompromised or suspected of having acute hepatitis C

3- Real-time PCR–based assays: preferred to follow up +ve anti-HCV assay

4- Liver biopsy

- Pathologic features:
    - Range from minimal periportal lymphocytic inflammation to active hepatitis with bridging fibrosis, hepatocyte necrosis, and cirrhosis; steatosis, lymphoid aggregates, and bile duct damage are frequent
    - These findings are common with other viral and nonviral causes of liver disease
- Value of liver biopsy:
    - Assessment of the severity of liver damage (grade of hepatic necroinflammation and stage of fibrosis)

- Detection of other potential coexisting diseases such as hemochromatosis, alcohol-induced injury, and nonalcoholic steatohepatitis
- Determination of the rate of disease progression in patients with a known date of infection or prior liver biopsy

- Indications for liver biopsy in chronic HCV

Indicated	Not indicated
- Genotypes 1, 4, 5, 6 (recommended) - onresponse or relapse after previous therapy	- Patient's desire for treatment even if no fibrosis - Contraindications to therapy - Genotypes 2 or 3 - High suspicion of cirrhosis

5- Noninvasive tests

- Should not replace liver biopsy in routine clinical practice
- Help in assessment of the extent of liver fibrosis
  - Direct or indirect markers of liver fibrosis (alone or in combination)
  - Transient elastography (FibroScan) measures liver stiffness and predicts significant fibrosis and cirrhosis accurately

Treatment

1- Goals of therapy

- The primary goal of therapy:
  - Eradication of infection early in the course of disease to prevent progression to end-stage liver disease and HCC
- The standard therapeutic end points
  - Are sustained biochemical and virologic responses, which are often accompanied by histologic improvement
- Additional goals
  - Prevention of transmission of the virus
  - Reduction of extrahepatic manifestations
  - Enhancement of quality of life

2- Indications

- All patients with chronic HCV with detectable serum HCV RNA and persistent elevation of ALT levels considered potential candidates for antiviral therapy
- In genotypes 1 and 4: moderate or severe necroinflammatory activity or more than portal fibrosis
- Symptomatic mixed cryoglobulinemia
- Controversial: patients with histologically mild chronic hepatitis

3- Contraindications: to antiviral therapy in chronic HCV infection

	Absolute	Relative
Peg-interferon	- Major uncontrolled psychiatric disorders (especially depressive illness) - Decompensated cirrhosis (unless LT is considered) - Solid organ transplantation other than liver - Cardiac arrhythmia. - Active auto-immune disease.	- Poorly-controlled DM. - Pancytopenia. - Chronic obstructive pulmonary disease. - Active alcohol or IV drug abuse. - Age ≥ 75 yr - Uncontrolled seizure disorder
Ribavirin	- Renal failure. - Anemia (Hb < 10 mg/dl). - Significant coronary heart disease. - Pregnancy risk - Breast feeding.	- Severe hypertension

4- Available drugs: combination of

- Peg-INF alfa-2a (180 µg/week) or Peg-INF alfa-2b (1.5 µg/kg/week) subcutaneous injection
- + Ribavirin: dosing is based on body weight
  - For genotype 1:

Patients < 75 kg body weight → Ribavirin 800-1400 mg/day with Peg- INF alfa-**2b**.

Patients < 75 kg body weight → Ribavirin 100-1200 mg/day with Peg-INF alfa-**2a**

Patients > 75 kg body weight → Ribavirin 100-1200 mg/day with Peg-INF alfa-**2a**

- For genotype 2 & 3:

  Fixed dose of 800 mg/day

5- Duration:

- Genotype 1: 48 weeks
  - Week 12 stopping rule: patients without early virological response unlikely to achieve sustained virological response
  - Shorter treatment duration: 24 weeks is possible in genotype 1 patients with rapid virological response & low viral load (< 600,000 IU/ml).
  - Longer treatment duration (72 weeks) possibly beneficial in slow responders
- Genotype 2 & 3: 24 weeks
  - Shorter treatment (12-16 weeks) is possible in genotype 2/3 achieving rapid virological response

6- Definitions of response to treatment:

- Rapid virological response (RVR): HCV-RNA gets undetectable by week 4
- Early virological response (EVR): ≥ 2 log decline in HCV-RNA by week 12
- Partial virological response: ≥ 2 log decline in HCV-RNA by week 12, but HCV-RNA detectable at week 24
- End of treatment (EOT) response: undetectable HCV-RNA at the end of treatment

- Sustained virological response (SVR): HCV-RNA negativity 12-24 weeks after the end of treatment
- Nonresponse: failure to achieve HCV RNA negativity at any time point during therapy
- Relapse: end of treatment response followed by return of HCV RNA after treatment discontinuation

7- **Efficacy:**

- Genotype 1&4: overall sustained virological response 42-52%.
- Genotype 2&3: overall sustained virological response 75-82%.
- Factors associated with therapeutic outcomes in chronic HCV:

Factor	Favorable therapeutic response	Impaired therapeutic response
Age	< 40 yr	≥ 40 yr
Gender	Female	Male
Genotype	2,3	1
BMI	Normal	> 30
Race	White	African American
Pretreatment HCV-**RNA**	< 800,000 IU/ml	≥ 800,000 IU/ml
ALT	++	+
Steatosis in liver biopsy sample	Absent	Present
Fibrosis in liver biopsy	Mild	Advanced
IL28B polymorphism	CC genotype	TT/CT genotype

8- **Adverse effects:**

Interferon	Ribavirin
1. Influenza-like syndrome. 2. Auto-immune reactions. 3. Depression (even suicidal). 4. Myelosuppression. 5. Hypo/hyperthyroidism.	Hemolysis (usually 2 gm fall in Hb). Teratogenicity.

6. Hair loss.	

9- **Long term follow up**

- Non-cirrhotic patients achieving SVR: ALT annually
- Cirrhotic patients achieving SVR: CBC, hepatic biochemical tests & U/S every 6 months
- Patients without SVR:
  - If cirrhotic: complete lab tests & U/S every 6 months
  - If non-cirrhotic: complete lab tests & U/S annually

10- **Liver transplantation**

- Chronic hepatitis C is the most common indication for liver transplantation
- Post-transplant recurrence of HCV RNA is universal
- Histologic evidence of liver injury is present in approximately 50% of patients after transplant at 1 year, and the proportion increases with follow-up
- Serologic assays underestimate the frequency of post-transplantation HCV infection, and virologic tests are required for diagnosis
- Histologic findings typical of post-transplant HCV infection include fatty infiltration, portal and parenchymal mononuclear infiltrates, and hepatocyte swelling and necrosis
- Interferon-based therapy ± ribavirin has been used to treat posttransplant HCV recurrence; transient reductions in serum HCV RNA levels have been observed, but sustained biochemical and virologic responses are uncommon (one-third or less).

11- **HCV treatment algorithms**

12- **Potential future therapy of chronic hepatitis C** [Protease inhibitors (telaprevir & boceprevir)]

- There is approval of a triple therapy in patients infected with HCV genotype 1 who are treatment-naïve or had nonresponse to a prior course of pegylated IFN-a and Ribavirin
- There is confirmation that a significantly higher proportion of naïve and non-responder patients with genotype 1 infection have had an SVR with this triple therapy
- In a proportion of patients with satisfactory early responses, treatment can be significantly shortened

Screening and counseling

1- Once a patient is determined to be **at risk**, HCV testing should be performed

2- Persons infected with HCV should be counseled on how to **avoid HCV transmission:**

- Avoid sharing dental or shaving equipment
- Cover bleeding wounds to prevent contact with others
- Discontinue illicit injection drugs
- Do not donate blood, organs, tissue, or semen
- Be aware that barrier protection is not needed in monogamous relationships
- Avoid alcohol intake
- For susceptible individuals, obtain hepatitis A and B vaccination

Interferon therapy [IFN]

Indications

1- Chronic hepatitis C (®)

2- Chronic hepatitis B (®)

3- Acute hepatitis C (®)

4- Chronic hepatitis D (®)

5- Hairy cell leukemia

6- Follicular lymphoma

7- Malignant melanoma

8- Condylomata acuminate

9- AIDS – related Kaposi's sarcoma

Contraindications

1- Leukopenia or thrombocytopenia

- Because of the potential for bone marrow suppression

2- Decompensated cirrhosis (unless LT is considered)

- Because it is rarely effective and may cause further decompensation of liver disease
- Also, platelets and WBCs are low
  - Portal HTN, HE and ascites
  - PT > , Bilirubin > and serum albumin <

3- Patients with severe depression, history of suicide attempt or ideation, psychosis, or personality disorders

- Should not be treated or should receive treatment only under the close monitoring of a psychiatrist

4- Patients with manic depression

- Do poorly with IFN therapy and should not be treated unless their psychiatric condition is well controlled and they are under the care of a psychiatrist.

5- Patients who continue to drink alcohol on a daily basis respond less to antiviral therapy

- Complete abstinence from alcohol during therapy is recommended.
- For patients who drink excessive amounts of alcohol, abstinence for a minimum of 6 months before initiation of therapy is required to maximize benefits of therapy

6- Autoimmune diseases such as rheumatoid arthritis, sarcoidosis, SLE and autoimmune hepatitis

- Relatively contraindicated
- But, absolutely contraindicated during activity (these disorders caused by overactive immune system which IFN stimulate further)

7- **Pregnancy:**

- If hepatitis C infection is diagnosed during pregnancy, treatment should be initiated only after delivery and breastfeeding have been completed

8- **Advanced comorbid conditions:**

- Hepatitis C infection progresses slowly over time.
- If the patient has a life expectancy of < 5 - 10 years, treating the hepatitis C infection is not likely to be of benefit

9- **Organ transplantation other than liver**:

- As the risk of rejection is increased with IFN.

10- **Cardiac arrhythmia**

11- **Relative contraindications:**

- Poorly-controlled DM
- Pancytopenia
- Chronic obstructive pulmonary disease
- Active alcohol or IV drug abuse
- Age ≥ 75 yr
- Uncontrolled seizure disorder
- Psoriasis: can worsen during therapy
- Some forms of eye diseases as IFN may cause slight problems

Side effects + Monitoring

1- **Bone marrow suppression:**

- Resulting in leukopenia or thrombocytopenia.
- CBC should be monitored periodically, and the dose is adjusted as needed.
- To avoid dose reductions, use of growth factors such as filgrastim for neutropenia should be considered

2- **Flu-like symptoms**, headaches, fever, rigors, arthralgias and myalgias:

- Evening administration and preinjection acetaminophen or ibuprofen can reduce the flu-like symptoms

3- **Depression:**

  - Depression requires close monitoring
  - Patients with a history of severe depression or suicidal ideation or attempts should not be treated with IFN
  - Patients who have required pharmacologic therapy for mild depression in the past may benefit from initiation of antidepressants before treatment with IFN
  - Selective serotonin reuptake inhibitors usually are successful in reversing IFN-associated depression
  - Close monitoring for suicidal ideation is mandatory

4- **Anxiety**

5- **Sexual dysfunction**

6- **Hair loss, insomnia**

7- **Fatigue**

8- **Hypothyroidism:**

  - Irreversible side effect of IFN.
  - Levels of TSH should be determined before initiation of therapy and at regular intervals during treatment

9- IFN is contraindicated during **pregnancy**

10- Ocular problems

11- Nausea, vomiting and weight loss

12- Pulmonary complications as interstitial fibrosis

13- Memory and concentration disturbances

Ribaverin therapy

Indications

1- **Chronic hepatitis C:** write indications and doses

2- **Thyroid cancer:**

    - Treatment of follicular, medullary, and anaplastic thyroid carcinoma and metastatic or locally advanced papillary thyroid cancer

3- **Hemorrhagic fever** (Lassa fever) with renal syndrome

4- **Severe RSV infection**

Contraindications

1- Because ribavirin must be used with IFN, **all contraindications to IFN** apply to treatment with ribavirin. In addition, there are specific contraindications to ribavirin

2- **Pregnancy** and unreliable method of contraception
    - An absolute contraindication because of the teratogenic potential

3- Also, **breast feeding** is an absolute contraindication

4- **Anemia and hemoglobinopathies**
    - Should be considered relative contraindications.
    - Extreme care should be exercised in treating such patients.
    - Hb < 10 g/dL is an absolute contraindication, as fall of 2 g usually occur rapidly with treatment.
    - As a rule, females with a hemoglobin less than 12 g/dL or males with less than 13 g/dL before therapy are at high risk of developing severe anemia during therapy

5- **Patients with known ischemic heart disease**
    - Should be treated with caution and monitored closely.
    - Significant disease is an absolute contraindication (anemia worse the condition)

6- **Patients with renal insufficiency**
    - Should not be treated with ribavirin because the development of severe, long-lasting, and life-threatening hemolysis is common (ribavirin is excreted via the kidney).

7- **Hypertension** is a relative contraindication

Side effects + Monitoring

1- **Hemolysis** and may rapidly lead to symptomatic **anemia**
   - A reduction in hemoglobin to 10 g/dL or less, if associated with symptoms, should trigger corrective action
   - Use of epoetin alfa to treat anemia is preferred to ribavirin dose reduction to maximize treatment efficacy
   - If the hemoglobin decreases to 8.5 g/dL or less, temporary discontinuation of therapy is advised
   - For patients with known ischemic cardiac disease, closer monitoring is recommended, with reduction or discontinuation of therapy if the hemoglobin decreases by more than 2 g/dL compared with baseline
   - Hemolysis can lead be life threatening for patients with ischemic heart disease or cerebral vascular disease

2- **Other side effects** from ribavirin include:
   - Rash, shortness of breath, nausea, sore throat, cough, and glossitis
   - The rash may be severe and require discontinuation of the medication

3- **Because ribavirin is teratogenic**, both male and female patients should be advised to practice effective contraception during therapy and for 6 months after completion

IL-28B polymorphism in HCV infection

IL-28B polymorphism:

1- Current standard care for hepatitis C infection is treatment with interferon and ribavirin

2- IL-28B (interferon lambda 3) is a family of class II cytokines that stimulate antiviral responses through a heterodimeric receptor that is distinct from the type I interferon

3- Unlike type I interferons, the target cell populations of interferon-lambda are restricted and mainly include epithelial cells and hepatocytes

4- Like interferon alpha, interferon lambda upregulates interferon stimulated genes (ISGs) by inducing JAK-STAT Pathway. However, interferon lambda binds to a receptor different from interferon alpha

5- Recent genome-wide association studies (GWAS) have shown that a genetic polymorphism at rs12979860 near IL28 gene on chromosome 19, encoding interferon-lambda-3, is associated with variable responses to the drugs

6- Also, a second polymorphism (rs8099917) identified in a similar region near the IL-28 gene which was strongly associated with response to combination treatment with interferon and ribavirin in Australian and Japanese patients, all infected with viral genotype 1. High rates of SVR are associated with rs8099917 TT genotype

Value in chronic hepatitis C:

1- CC genotype of IL-28B is associated with 2-3 fold increases in sustained virologic response (SVR) as compared with either CT or TT genotype

2- SNPs of IL28B are useful baseline predictors for virological response in patients infected with genotype 1 or 4 HCV when treated with PegIFN/RBV, but not in patients with genotype 2 or 3 HCV

3- Therefore, determination of IL28B genotype may be necessary only in HCV genotype 1 or 4 patients

Value in acute hepatitis C:

1- Genetic variations in IL28B region may predict who will have enough innate immune response to spontaneously clear virus after acute hepatitis C

2- Early therapeutic intervention could be recommended for individuals with unfavourable IL-28B genotypes

Studies results:

1- A study published in Nature analysed the data on more than 1,600 participants in a clinical trial IDEAL which compared the 2a and 2b forms of pegylated interferon in patients infected with HCV genotype 1

2- Genome-wide association studies were performed on tissue samples from these individuals, correlating their virologic responses to a large number of gene polymorphisms

3- SVR rates in patients with IL-28B genotype CC were 69% in Caucasians, 48% in African-Americans, and 56% in Hispanics. These response rates were two fold higher than genotypes TC and TT

4- IL-28B CC patients also responded more quickly to treatment within each ethnic group compared with the TC and TT genotypes. This genotype was seen in 77% of patients with rapid virologic response (RVR). Moreover, CC genotype predicted sustained responses in white patients who had not shown RVR. In such patients, 66% of those with the CC type eventually obtained a sustained response, compared with 31% of TC and 24% of TT genotypes

5- Patients infected with viral genotype 2/3 already show good response to the treatment. Knowing IL-28B polymorphism in such cases may be of value only in those patients who do not achieve a RVR

Recommendations

1- IL-28B genotype testing would become part of the standard of care once a test becomes clinically available. Genetic analysis of the host will be able to predict which patients are more likely to respond to treatment. IL-28B genotype is only one of many factors that can influence response rates to pegylated interferon and ribavirin therapy in HCV infection and should be interpreted in the context of other clinical factors predicting sustained response rates including HCV genotype, viral loads, ethnicity, baseline liver fibrosis, and fasting blood sugar etc.

2- For those patients infected with difficult-to-treat genotype 1 or 4 HCV and also bearing rs12979860 non-CC genotype or rs8099917 non-TT genotype, it is urgent to develop more effective therapy strategies

3- Association of single nucleotide polymorphism in IL-28B gene region with pegylated interferon treatment outcome raises the possibility of using IL-28B (interferon lambda) as a therapeutic agent against hepatitis C

Extrahepatic manifestations of HCV

Incidence

1- Up to **40% - 74%** of patients develop at least one extrahepatic manifestation during the course of their disease

2- **Rheumatologic and cutaneous** manifestations are the most common

3- Some manifestations are more common and well documented, as **cryoglobulinemia**, while others are infrequent or their association with hepatitis C has not yet been proven

4- The vast majority of people with hepatitis C may **never experience the more severe types** of these extrahepatic manifestations

5- Many of these conditions are related to **cryoglobulin** (an abnormal blood protein) production

The most common manifestations

[Many of these conditions are related to cryoglobulin (an abnormal blood protein) production]

1- **R**heumatologic and **c**utaneous manifestations
2- **F**atigue
3- **T**hyroid disease
4- **P**aresthesias
5- **M**yalgias
6- **P**ruritus
7- **I**nsulin resistance
8- Type II **d**iabetes
9- **K**idney disease

Proven and possible associations of HCV

Proven associations	Possible associations
1- Autoimmune thyroiditis	1- Chronic polyarthritis
2- B-cell non Hodgkin's lymphoma	2- Idiopathic pulmonary fibrosis
3- Diabetes mellitus	3- Non-cryoglobulinemic nephropathies
4- Lichen planus	4- Sicca syndrome
5- Mixed cryoglobulinemia	5- Thyroid cancer
6- Monoclonal gammopathies	6- Renal cell carcinoma
7- Porphyria cutanea tarda	7- Vitiligo

Treatment

Many extrahepatic manifestations of HCV are treated by treating the underlying cause–hepatitis C–with **pegylated interferon and ribavirin**

Diagnosis

1- Laboratory testes

- **Urinalysis:** Abnormalities may represent evidence of renal disease
- **CBC:** Leukocytosis may be a manifestation of concomitant infection or leukemia. Anemia or thrombocytopenia may be present
- **Serum chemistry:** Patients with renal insufficiency may present with elevated serum creatinine levels and electrolyte abnormalities
- **RF:** positive in types II and III cryoglobulinemia
- **ANA:** indicated upon clinical suspicion of underlying connective-tissue disease (SLE, Sjögren syndrome)
- **ESR:** Elevations may be secondary to rouleaux formation
- **Complement evaluation** (CH50, C3, C4): Patients with cryoglobulinemia may display hypocomplementemia (especially low C4 levels).
- **Other studies:** Consider serum protein electrophoresis (SPEP), urine protein electrophoresis (UPEP), and quantitative immunoglobulin upon suspicion for underlying gammopathy
- **Serum viscosity:** Measure serum viscosity if symptoms warrant
- **Further diagnostic** laboratory tests: patients with mixed cryoglobulinemia associated with HCV infection have elevated levels of

interferon-inducible protein 10 and that these levels correlate with disease activity

- **Serum cryoglobulin** (see below)
- Fasting and postprandial **blood glucose**
- **TSH, T3 and T4**

2- **Imaging**

- **Chest X-ray:** may reveal interstitial involvement or pleural effusions
- **CT:** if high suspicion of underlying malignancy
- **Transesophageal echocardiography:** should be obtained if bacterial endocarditis is suspected
- **Angiography:** if there is evidence of vasculitis

3- **Procedures**

- **Tissue biopsy:** may be required for diagnosis when patients with vasculitis, renal disease, or both are evaluated
- **Electromyography** and nerve conduction studies: may be used to confirm neuropathy when history or physical examination findings are suggestive
- **Further diagnostic procedures** (e.g. bone marrow biopsy, liver or kidney biopsy) as needed

Extrahepatic manifestations

1- **Fatigue**

- One of the most common symptoms of hepatitis
- Caused both by the body's immune response to hepatitis C as well as by the direct affect of the virus on the body

2- **Cryoglobulinemia**

- **Incidence**:
  - One of the most common disorders associated with hepatitis C

- Cryoglobulins can be found in 20-50% of patients with HCV, but clinical manifestations are reported only in 5-10% of these patients and more common in patients with cirrhosis

- **Definition:**
  - Cryoglobulinemia is a blood disorder caused by abnormal proteins in the blood called cryoglobulins that precipitate or clump together when blood is chilled and then dissolve when warmed.
  - These proteins can be deposited in the small and medium sized blood vessels, which restricts blood flow and can lead to further problems
- **Types:**
  - Type I: are mostly found in patients with lymphoproliferative disorders (e.g. multiple myeloma, B-cell lymphoma)
  - Type II & III: are highly prevalent in patients with chronic HCV infection
- **Evaluation for serum cryoglobulins**
  - The blood specimen must be obtained in warm tubes (37°C) in the absence of anticoagulants
  - Allow the blood sample to clot before removal of serum with centrifugation (at 37°C).
  - The period required for the serum sample to incubate (at 4°C) depends on the type of cryoglobulin present, as follows:

    Type I tends to precipitate within the first 24 hours (at concentrations >5 mg/mL).

    Type III cryoglobulins may require 7 days to precipitate a small sample (< 1 mg/mL).
  - Repeat centrifugation to determine cryocrit (volume of precipitate as a percentage of original serum volume).
  - Cryoglobulin concentration may be determined via spectrophotometric analysis. Specific immunologic assays may be used to identify cryoglobulin components (immunoglobulins, light chains, clonality).
- **Diagnosis is made when**
  - Rheumatoid factor is detected

- Cryoglobulins are present
- Complement levels are low

- **Specific clinical manifestations associated with type I cryoglobulinemia** are related to hyperviscosity and thrombosis, and include
  - Acrocyanosis
  - Retinal hemorrhage
  - Severe Raynaud phenomenon with digital ulceration
  - Livedo reticularis
  - Purpura
  - Arterial thrombosis
- **Specific clinical manifestations associated with types II and III cryoglobulinemia** include
  - Joint involvement (usually, arthralgias in the proximal interphalangeal [PIP] joints, metacarpophalangeal [MCP] joints, knees, and ankles)
  - Fatigue
  - Myalgias
  - Renal immune-complex disease (nephropathy e.g. hematuria, proteinuria, edema and renal impairment)
  - Cutaneous vasculitis
  - Peripheral neuropathy
- **Cryoglobulinemia can affect** the skin, kidneys, nerves and joints
- **Treatment:**
  - Consists of treatment of the underlying disease (hepatitis C) [resolves in patients who achieve SVR]
  - NSAIDS: if arthralgias or fatigue present
  - Immunosuppressive drugs
  - Plasmapheresis + concomitant use of high dose steroid or cytotoxic drugs to prevent rebound phenomenon after plasmapheresis

3- Rheumatologic manifestations:

- **Arthralgia** is a common symptom
- **Arthritis**
  - 4% of the HCV population

    - Polyarthritis similar to rheumatoid arthritis but is less serious
    - Or mono-oligoarthritis affects the medium and large sized joints – typically the ankles
- **Systemic Lupus Erythematosus (SLE)**
    - There are many strategies for managing SLE including the use of NSAIDs, acetaminophen, corticosterioids, immunomodulating drugs, and anticoagulants
- **Fibromyalgia**
    - Characterized by aches, pain, stiffness, soft tissue tenderness, general fatigue and sleep disturbances
    - Pain is the most common symptom of fibromyalgia and it is usually confined to muscles and ligaments

4- Cutaneous manifestations

- **Spider Nevi**
    - Small red dots with radiating lines resembling a spider web
    - Found anywhere on the body but usually affects the face and trunk
- **Lichen Planus**
    - Skin disorder characterized by small elevated bumps or pimples and usually appears on flexor surfaces–arms, trunk, genitals, nails and scalp
    - Symptoms can include scaling, itching, hair loss, skin lesions, plaque, and pain
    - Cause HCV replication in epithelial cells
    - Treatment: Cortisone creams/ointments and cortisone injections are used for managing the symptoms. Avoid substances that can trigger a flare-up of symptoms including alcohol, tobacco, spicy foods, peppermint, cinnamon, citrus type foods and stressful situations
- **Lichen Myxoedematosus (LM)**
    - Rare chronic condition that has been linked to HIV infection, hepatitis C infection, and exposure to toxic oil and contaminated L-tryptophan
    - Characterized by small papules (bumps) that affect the face, trunk and extremities that can progress on to skin tightening and hardening

- **Porphyria Cutanea Tarda (PCT)**
    - It's a disorder of heme biosynthetic pathway leading to accumulation of toxic metabolites (reduced activity of an enzyme resulting in an overproduction and build up of the protein uroporphyrinogen in the blood and urine of patients) and hepatitis C has been suggested as a cause (> 50% in southern Europe)
    - Other causes include hereditary hemochromatosis, heavy alcohol use and estrogens
    - Develop in areas that are exposed to the sun with resulting skin lesions (blisters) on the hands, forearms, back of the neck and face & cause also photosensitization
    - PCT can also cause skin discoloration, either darkening or lightening of the skin, increased facial hair, thickening of the skin, and alopecia (hair loss).
    - Diagnosis: 24-hrs urine measurements of aminolevulinic acid (ALA) or porphobilinogen (PBG): levels are 3-10 times the upper limit of normal (7 mg) & Urine uroporphyrin levels are elevated & liver enzymes may be elevated
    - Treatment of PCT: can involve phlebotomy, dietary iron restriction, reducing alcohol consumption, avoiding exposure to the sun or the use of sunscreen, and avoiding or minimizing estrogen exposure. Chloroquine is useful in PCT as it forms complexes with uroporphyrin
- **Pruritus**
    - Is one of the most common symptoms reported by people with hepatitis C (15%), but is more commonly found in people with end stage liver disease
    - May be localized or generalized
    - Cause: It can be related to high bilirubin levels, autoimmune disease or dry skin, and can be a side effect of treatment
    - Use of moisturizing lotions, oatmeal baths or lotions, antihistamines, and cortisone creams and opiate drugs can help
- **Vitiligo**

  - Loss of pigmentation – usually around the mouth, eyes, nose, elbows, knees and wrists

5- Hematologic manifestations

- **Immune Thrombocytopenic Purpura (ITP)**
  - Symptoms: easy bruising , petiche , ecchymosis and bleeding in severe cases
- **Thrombocytopenia** : can also occur due to interferon treatment
- **Vasculitis** (essential cryoglobulinemic vasculitis)
  - Purpura, petechiae usually affects the lower extremities of the body
  - Other symptoms include fever, itching welts, muscle ache and pain and enlarged lymph nodes as well as peripheral neuropathy
  - Treatment: interferon + ribavirin & immunosuppressive drugs
  - Skin biopsy will show inflammation of the small blood vessels indicating vasculitis
- **Waldenstrom Macroglobulinemia (WM)**: chronic low-grade type of cancer of the lymph cells
- **Multiple Myeloma:** anemia, infections, and bleeding
- **Neutropenia**: leads to ↑ risk of infections, and may caused also by interferon
- **Non-Hodgkin's Lymphomas:** uncommon, remission occure with interferon and ribaverin

6- Kidney disease

- **Membranoproliferative Glomerulonephritis (MPGN)**
  - Usually (but not always) associated with cryoglobulinemia
  - Symptoms include weakness, edema and arterial hypertension
  - Treatment: if there is severe kidney impairment, ribavirin should be avoided
- **Membranous Nephropathy**
  - Not associated with cryoglobulinemia
  - Cause: deposition of HCV antibodies and viral particles in the kidneys causing damage

- Treatment consists of interferon plus ribavirin. If there is severe kidney damage then the use of ribavirin should be avoided

7- **Lung diseases and abnormalities**

- Idiopathic Pulmonary Fibrosis
- COPD (chronic bronchitis and emphysema).
- Asthma
- Hypoxemia
- Interferon can also cause various lung abnormalities

8- **Thyroid disease**

- Autoimmune thyroiditis
- Thyroid autoantibodies (25%)
- Hypothyroidism (13%)
- Hyperthyroidism
- May be thyroid cancer
- HCV treatment can also induce thyroid disease, but thyroid function will return to normal for about 95% of people who develop treatment-related hypothyroidism when treatment is stopped

9- **D.M**

- **Insulin Resistance (IR)**
  - Inability of cells to absorb glucose. This leads to the pancreas releasing more insulin so there is an excess amount of both glucose and insulin in the bloodstream
  - IR lowers treatment response and can speed up HCV disease progression
  - There is strong argument about the fact that viral eradication after antiviral therapy leads to improvement of insulin resistance
- **Type 2 Diabetes**

10- **Neurological manifestations**

- **Paresthesia**
- **Peripheral Neuropathy (PN)**

- Characterized by numbness, burning, pins and needles sensations, crawling skin, and itching that occurs most often in the hands and feet, but can appear in other areas of the body
- People with HCV-related PN should be tested for Cryoglobulinemia
- 15.3% of people with HCV were diagnosed with PN

11- Other manifestations

- Behcet's Disease: ulcerations in the eyes, mouth and genitals but can also affect any organ of the body
- Canities; premature graying of the hair, but is uncommon
- Hypertrophic Cardiomyopathy: Very rare
- Mooren Corneal Ulceration: pain, inflammation, tearing and loss of sight
- Raynaud's Syndrome
- Sialadenitis
- Sjogren's Syndrome: autoimmune disease that affects the eyes and mouth, making them dry

Fatty liver and NASH

Definitions

1- **Nonalcoholic fatty liver disease:**

- Excessive liver triglyceride accumulation when alcohol consumption is minimal (less than 2-4 drinks daily).

2- **Nonalcoholic fatty liver disease:**

- Is the umbrella term that includes both steatosis without inflammation and NASH

3- **NASH is diagnosed when:**

- liver biopsy specimen shows steatosis and characteristic necroinflammatory changes in a patient who has fewer than 2-4 drinks daily
- The presence of fibrosis is not required, but characteristic perisinusoidal fibrosis supports a diagnosis of steatohepatitis

4- **NASH is not a diagnosis of exclusion**

- It can often be found in the presence of other liver diseases such as chronic hepatitis C

PAathogenesis of NASH

- ■ Lipotoxic injury to hepatocytes caused by nontriglyceride metabolites of free fatty acids
- ■ Triglyceride in the lipid droplets may a protective response to store fatty acids in an inert form
- ■ Possible metabolites of free fatty acids that cause lipotoxic injury include: ceramides, diacylglycerols, lysophosphatidyl choline species, and phosphatidic acid species

1- **Increased peripheral mobilization of fatty acids**

- Adipose tissue releases free fatty acids in response to (cAMP)–mediated signaling from glucagon, epinephrine, and ACTH
- Released fatty acids are transported to the liver bound to albumin in the circulation
- Insulin is a major inhibitory signal that normally prevents adipose tissue lipolysis after meals; adipocyte insulin resistance allows inappropriate postprandial lipolysis in adipose tissue with release of free fatty acids into the circulation
- Prolonged starvation is associated with appropriate release of fat from peripheral stores that can overwhelm the liver's ability to handle it, thus leading to steatosis and NASH

2- Increased hepatic synthesis of fatty acids

- The liver disposes excess carbohydrates, especially fructose, by converting carbohydrate to fatty acids through de novo lipogenesis; excess carbohydrates from dietary sources (e.g., sugarsweetened beverages) or provided parenterally (e.g., total parenteral nutrition) predispose to hepatic lipotoxicity

3- Impaired hepatic catabolism of fatty acids

- Impaired mitochondrial beta-oxidation of fatty acids is a major factor in alcoholic steatosis and has also been shown to contribute to the development of NASH
- Factors that cause microvesicular steatosis may do so through impaired mitochondrial function (e.g., valproic acid, alcohol, and acute fatty liver of pregnancy).
- Other oxidative pathways (cytochrome P-450, peroxisomal) facilitate disposal of fatty acids

4- Impaired synthesis of triglyceride and its secretion as VLDL from the liver

- Fatty acids delivered to the liver but not metabolized are reesterified to form triglycerides
- Fatty acid esterification to triglyceride ensures that the level of fatty acids within hepatocytes remains low, thus averting cellular injury from fatty acid metabolites

- Monounsaturated fatty acids (MUFAs) are needed to make triglyceride; impaired MUFA synthesis in the liver may predispose to lipotoxicity
- Once triglyceride is formed, various components are needed to form and secrete intact VLDL
- Any deficiency or metabolic aberration that interferes with any one of these steps can cause accumulation of hepatic triglyceride and hepatic steatosis
- Autophagy may be an important pathway of handling accumulated triglyceride to release free fatty acids by lysosomal lipases in hepatocytes

Clinical features

1- Symptoms

- Usually asymptomatic: whereas patients with alcoholic hepatitis are nearly always symptomatic
- Right upper quadrant pain or fullness of varying severity:
  - Occurs in 1/3 of patients with NAFLD
  - The cause may be liver capsule distention
- Accidental diagnosis: occasionally when imaging studies needed to exclude potential intrahepatic or biliary causes of right upper quadrant pain

2- Signs

- Hepatomegaly:
  - Common
  - Difficult to detect on physical examination of the obese patient
- Signs of chronic liver disease point to the presence of cirrhosis: as
  - Spider telangiectasias
  - Jaundice
  - Muscle wasting
  - Ascites
- Acanthosis nigricans:
  - Increased pigmentation around the neck and on the elbows, knuckles or other joints

- Associated with insulin resistance

Risk factors

1- **Insulin resistance**

- Most patients with NAFLD have underlying insulin resistance
- NAFLD may be the first indication that a child or adult has insulin resistance
- Most risk factors for NAFLD are associated with insulin resistance
- Severe insulin resistance is a risk factor for NASH
- Body habitus and frequency of hepatic steatosis

Body habitus	Hepatic steatosis (%)
Normal	21
>10% over ideal body weight	75
Morbidly obese	90–95

2- **Obesity**

- An increased ratio of abdominal fat to hip fat predicts NAFLD
- NASH is found in 8% - 20% of obese individuals with NAFLD
- NAFLD occurs in 90% - 95% of severely obese children and adults

3- **Type 2 diabetes mellitus**

- NAFLD is unusual in type 1 diabetes mellitus unless glycemic control is poor or the patient is also obese and insulin resistant
- Type 2 diabetes mellitus is a risk factor for NASH in patients with NAFLD

4- **Lipid abnormalities**

- Fasting hypertriglyceridemia partially reflects increased trafficking of fat through the liver and increased hepatic secretion of VLDL and thus is commonly found in NAFLD; this condition does not directly cause NAFLD
- The role of hypercholesterolemia in the causation of NAFLD is uncertain; the goal of treating hypercholesterolemia is reduction of cardiovascular risks

5- **Gender**

- Female gender is *not* a risk factor for NAFLD
- Steatosis is equally prevalent among male and female patients on computed tomography (CT) and at autopsy
- A greater prevalence of NASH in women has not been confirmed by clinical studies

6- **Medications**

- Tamoxifen can cause NASH; the decision to stop tamoxifen should be individualized depending on the severity of liver disease and the risk of recurrent breast cancer
- Corticosteroids have been implicated as contributing to NAFLD, but supporting data are weak

7- **Lifestyle**

- Sedentary behavior is associated with insulin resistance and NAFLD
- Excessive consumption of high-fructose corn syrup, such as in soft drinks, is associated with insulin resistance and NAFLD

Causes of NASH

Nutritional abnormalities	- Obesity - Total parenteral nutrition - Choline deficiency - Rapid weight loss - Kwashiorkor
Drugs	- Tamoxifen - Corticosteroids - Chloroquine
Metabolic diseases	- Insulin resistance - Abetalipoproteinemia - Hypobetalipoproteinemia - Wilson disease - Weber-Christian disease
Surgical alterations of gastrointestinal anatomy	- Jejunoileal bypass - Jejunocolic bypass - Extensive small bowel loss - Gastroplasty
Occupational	- Hydrocarbons

exposure	

Diagnosis

History

1- A patient suspected of having NASH should be **interviewed regarding the following**

- Alcohol consumption
- Exercise habits and barriers to regular exercise
- Sugar-sweetened beverage consumption
- Frequency of eating fast food
- History of gestational diabetes mellitus
- Family history of diabetes mellitus

2- The nature and frequency of **right upper quadrant abdominal pain**

Laboratory features

1- Elevated AST and ALT levels:

- Are commonly the only biochemical indicators

2- ALT and AST: can be normal

3- The AST/ALT ratio can be helpful in distinguishing alcoholic hepatitis from NAFLD or NASH:

Steatohepatitis and serum aminotransferase patterns	
Alcoholic hepatitis	AST > ALT, typically >2:1 ratio
Nonalcoholic steatohepatitis (without cirrhosis)	ALT > AST, sometimes >2:1 ratio
Nonalcoholic steatohepatitis (with cirrhosis)	Typically, AST > ALT

4- ALT and AST levels:

- Often normalize as NASH progresses to cirrhosis

5- Serum alkaline phosphatase:

- May be elevated up to twice ULN

6- Viral, autoimmune, and metabolic causes of liver disease:

- Must be evaluated as potential contributors to elevated aminotransferase levels

Imaging

- ■ Imaging studies cannot distinguish benign steatosis from NASH
- ■ NASH is usually diffuse, whereas steatosis can be either focal or diffuse

1- U/S

- The liver is echogenic or "bright."
- Detects steatosis only when fat accumulation is substantial
- Cirrhosis can also cause an echogenic appearance of the liver, but the texture is typically coarser

2- CT

- A liver with steatosis is low in density compared with the spleen on noncontrast images

3- MRI

- This imaging technique is the most sensitive noninvasive measure of liver fat
- Phase shifting can be useful for identifying focal fat based on its loss of intensity on T1-weighted images

4- Focal fat

- In 1/3 of patients with CT evidence of hepatic steatosis
- It can be peripheral (especially in the diabetic patient receiving insulin by peritoneal dialysis), central, or periportal
- It is typically aspherical or geometric in shape
- It does not exert a mass effect on adjacent structures
- Fine-needle biopsy occasionally is needed to establish the diagnosis

5-Focal sparing

- Regions of normal liver in an otherwise steatotic liver

- It appears relatively hypoechoic by U/S (compared with surrounding bright liver)
- It appears relatively hyperdense by CT
- The shape is typically geometric
- The location is commonly in the caudate lobe or adjacent to the gallbladder
- It can be caused by an aberrant gastric vein draining directly into the liver that spares an area of insulin-rich portal blood

6- Problems identifying other lesions in the steatotic liver

- Hemangiomas: which are usually characteristically hyperechoic by U/S, can appear relatively hypoechoic in a steatotic liver
- Identifying dilatation of intrahepatic bile ducts: can be difficult because of loss of contrast between the usually hyperechoic bile duct wall and the liver parenchyma

Liver biopsy

1- Indication:

- Unexplained elevation of aminotransferase levels

2- Should not be delayed:

- Unless a therapeutic trial of discontinuance of specific medications, aggressive lifestyle modification, or avoidance of occupational exposures is planned

3- Usually not indicated if:

- Imaging suggests steatosis and aminotransferase levels are normal

4- Histologic findings in nonalcoholic steatohepatitis

- Steatosis: Fat droplets (triglyceride) within hepatocytes can be large, displacing cellular contents to the periphery
- Inflammation:
  - Mixed neutrophilic and mononuclear cell infiltrates within the lobule

- Portal chronic inflammation can occur, especially in children and after treatment
- Ballooning enlargement of hepatocytes with rarefication of cytoplasmic contents is a marker of hepatocyte injury

- Mallory-Denk bodies:
  - Eosinophilic cytoplasmic aggregates of keratins typically smaller than those seen in alcoholic hepatitis
  - Usually found in ballooned hepatocytes
- Glycogen nuclei: clear intranuclear vacuoles fill the nucleus
- Fibrosis:
  - Similar to alcoholic liver disease, with perivenular deposition around the central vein and a "chicken wire" pattern of sinusoidal fibrosis
  - It occurs in approximately 1/3 of patients with NASH and signifies a risk for progression to end-stage liver disease
  - It is staged as 1 (perisinusoidal or periportal only), 2 (perisinusoidal and periportal), 3 (bridging), or 4 (cirrhosis).

Prognosis

1- Steatosis

- Steatosis alone is a benign condition, although it may be associated with clinically significant right upper quadrant abdominal pain

2- NASH

- The risk of fibrosis and cirrhosis is 10% - 50%
- The risk of developing cirrhosis when fibrosis is absent on initial biopsy is low
- HCC is increasingly recognized in patients with advanced NASH with fibrosis or cirrhosis

Treatment

1- Weight loss and exercise

- Gradual and sustained weight loss → results in resolution of steatosis and normalization of aminotransferase levels

- Weight loss achieved with protein malnutrition → does not improve hepatic steatosis
- Weight loss achieved with bariatric surgery → improves NASH, but patients must adhere to postoperative dietary guidance to avoid nutritional deficiencies
- Improved glycemic control in type 2 diabetes mellitus without weight loss → is not helpful
- Regular exercise → improves insulin sensitivity and improves NAFLD

2- Medications

■ No medications are approved for the treatment of NASH. The following drugs have been examined in clinical trials:

- Thiazolidinediones:
  - Appear to be beneficial for some patients, probably by improving adipocyte insulin sensitivity and preventing inappropriate lipolysis
  - Side effects include weight gain, exacerbation of heart failure, and possibly osteoporosis
- Vitamin E → may be helpful in some patients
- Other agents under evaluation include
  - Metformin
  - High-dose ursodiol
  - Omega-3 fatty acids
  - Pentoxifylline, exenatide
  - Silymarin
- Statin use → not contraindicated in patients with NASH

Alcoholic liver disease

Risk factors

1- **Amount & duration of alcohol intake:**
  - Amount ingested and duration of intake correlates with the incidence of alcohol-related liver disease
  - Once a threshold level of consumption is exceeded (**60-80 g/day for men** and **20 g/day for women**), the risk of hepatotoxicity increases dramatically

2- **Nutrition:**
  - Ethanol interferes with intestinal absorption and storage of nutrients and reduces appetite for nonalcoholic sources of calories.
  - This may result in deficiencies of protein, vitamins, and minerals

3- **Gender:**
  - Gastric mucosal alcohol dehydrogenase activity is lower in women than in men; allowing greater hepatic metabolism of ingested alcohol in women that's why women experience more toxicity per dose than men

4- **Genetic variability** in alcohol-metabolizing enzymes:
  - Polymorphisms of the alcohol dehydrogenase and aldehyde dehydrogenase enzymes seem to protect certain individuals from ethanol toxicity

- For example, Asians frequently inherit a ‘slow’ aldehyde dehydrogenase isoenzyme, thereby increasing serum levels of acetaldehyde. This causes flushing, nausea, and dysphoria (disulfiram-like reaction), and this may explain why habitual alcohol use and alcoholic liver disease are rare in Asians

5- Cofactors that may influence progression of ALD:

- Viral hepatitis:
    - Acute and chronic hepatitis B or C accelerates the progression of alcoholic liver disease
    - The risk of cirrhosis was 10-fold higher among heavy drinkers with chronic hepatitis C than among those with no evidence of HCV infection
    - In addition, alcohol and HCV act synergistically in the development of hepatocellular carcinoma
- Obesity:
    - The risk of liver disease is 2-3 times higher in drinkers who are obese than in drinkers who aren’t
    - Obesity also appears to be an independent risk factor for both alcoholic hepatitis and cirrhosis
- Smoking:
    - Cigarette smoking has been shown to accelerate the progression of fibrosis in patients with alcoholic liver disease
- Concurrent exposure to drugs or toxins:
    - Chronic consumption of alcohol induces the activity of microsomal enzymes, potentiating the metabolism of drugs
    - For example, therapeutic doses of acetaminophen can cause severe hepatic damage in alcoholic individuals; similarly, tolbutamine, isoniazid, and industrial solvents accelerate alcoholic liver disease
- Other cofactors:

- Accelerated disease progression is likely when alcohol abuse is accompanied by one or more of the following: a family history of alcoholic liver disease, hemochromatosis, Wilson disease, or alpha-$_1$ antitrypsin deficiency

Pathology

1- Fatty change

- The metabolism of alcohol invariably produces fat in the liver, mainly in zone 3. This is minimal with small amounts of alcohol, but with larger amounts the cells become swollen with fat (steatosis).
- There is no liver cell damage; the fat disappears on stopping alcohol

2- Alcoholic hepatitis

- In addition to fatty change there is infiltration by polymorphonuclear leucocytes and hepatocyte necrosis mainly in zone 3
- Dense cytoplasmic inclusions called Mallory bodies are sometimes seen in hepatocytes and giant mitochondria are also a feature
- Mallory bodies are suggestive of, but not specific for, alcoholic damage as they can be found in other liver disease, such as Wilson's disease and PBC. If alcohol consumption continues, alcoholic hepatitis may progress to cirrhosis

3- Alcoholic cirrhosis

- Alcoholic liver damage is typically associated with the deposition of collagen around the terminal hepatic vein (i.e. perivenular fibrosis) and along the sinusoids resulting in a 'chicken wire' pattern of scarring that is rarely seen in other types of cirrhosis
- Chronic consumption of alcohol also impairs the regenerative response that is normally triggered by liver cell death resulting in nodules of regenerating parenchyma that are small. For this reason, **micronodular cirrhosis** is seen in actively drinking patients

Clinical features

History

1- A history of habitual alcohol consumption is useful in suggesting alcohol as the cause of liver disease
2- The type of alcoholic beverage consumed does not influence the likelihood of developing hepatotoxicity
3- Exclusion of other potential causes of liver injury is mandatory

Physical findings

1- The clinical features are variable, ranging from a complete absence of symptoms to the florid features of advanced parenchymal cell failure and portal hypertension
2- Physical findings include:
  - Alcohol-related including:
    - Fever
    - Weakness
    - Anorexia, nausea and vomiting, malaise
    - Confusion
    - Sleep–wake cycle alterations
    - Cachexia
    - Enlarged parotid and lacrimal glands
    - Dupuytren's contractures
  - Liver-related including:
    - Enlarged liver (often tender hepatomegaly)
    - Splenomegaly
    - Jaundice
    - Spider angiomata, palmer erythema
    - Hypogonadism or gynecomastia

Diagnosis

■ The diagnosis of ALD is typically established clinically in patients with evidence of liver disease and history of significant alcohol use

Laboratory abnormalities

1- Fatty liver:

- CBC: macrocytic anemia (an elevated MCV often indicates heavy drinking).
- Liver biochemistry:
    - Only $^1/_3$ of hospitalized patients with fatty liver have laboratory abnormalities, which usually consist of mild increases in serum AST and ALT levels
    - The γ-GT level is a sensitive test for determining whether the patient is taking alcohol
    - With severe fatty infiltration, marked changes in liver biochemistry can occur

2- Alcoholic hepatitis:

- CBC: shows macrocytic anemia, thrombocytopenia, and leucocytosis occasionally to levels consistent with a leukemoid state
- Liver biochemistry: is markedly changed
    - Bilirubin → may be elevated up to 20-40 mg/dl
    - AST and ALT → elevated (Serum AST levels are almost always < 300 to 500 U/L and are typically associated with trivial elevation of serum ALT levels, resulting in an AST/ALT ratio > 2, which is characteristic of alcoholic liver disease because of deficiency of pyridoxal 5′ phosphate "a cofactor of aminotransferases" in alcoholic patients).
    - Alkaline phosphatase → Normal or increased to < 3 times normal
    - Prothrombin time (PT) → prolonged
    - Albumin → normal or decreased
- Others:
    - Triglycerides → Typically increased, especially in active drinkers
    - Potassium, phosphate, magnesium → often, deficient in active drinkers

- Glucose → Hyperglycemia is common

3- **Alcoholic cirrhosis:**

■ Laboratory tests may be completely normal in patients with early compensated alcoholic cirrhosis. On the other hand, in advanced liver disease, many abnormalities are usually present:

- CBC: thrombocytopenia and anemia either due to
  - Chronic GI blood loss
  - Nutritional deficiencies
  - Hypersplenism related to portal hypertension
  - Direct suppressive effect of alcohol on the bone marrow
  - **Zieve's syndrome**: A unique form of hemolytic anemia (with spur cells and acanthocytes) can occur in patients with severe alcoholic hepatitis
- Liver biochemistry:
  - Bilirubin → elevated
  - AST and ALT → elevated with AST/ALT ration > 2
  - Alkaline phosphatase → elevated
  - Prothrombin time (PT) → prolonged and usually do not respond to administration of parenteral vitamin K
  - Albumin → usually decreased

Imaging

1- Not helpful in implicating alcohol as the cause of liver disease

2- Although it's helpful in the following:

- It detects Ascites, biliary dilatations
- Screening for HCC
- Duplex Doppler U/S can further assess hepatic and portal vein patency

Liver biopsy

1- Not necessary for the diagnosis of alcoholic liver disease

2- But it's helpful in:

- Confirming the diagnosis

- Assessing severity of liver disease
- Excluding other contributing factors
- Staging of fibrosis

Indices of liver dysfunction for alcoholic hepatitis:

1- **Maddrey's discriminant function (DF):**
   - DF = 4.6 × (the difference between the patient's & control prothrombin time) + serum bilirubin
   - Patients with a DF > 32 have a 50% chance of dying during current hospitalization
   - This index offers the advantage of few variables and easy calculation

2- **Model for End-stage Liver Disease (MELD):**
   - A MELD score > 18 indicates a worse prognosis in alcoholic hepatitis

3- **Early change in bilirubin level and Lille score:**
   - A decrease in total bilirubin level at 7 days indicates improving liver function and predicts increased 6-month survival (82.8% versus 5.8%).
   - If total bilirubin doesn't decrease at 7 days the eventual response to steroids is low and steroids can likely be discontinued
   - Lille score is a composite score combining pretreatment parameters with response of bilirubin after 7 days of corticosteroids. A score > 0.45 indicates a lack of response to steroids and poor 6-month survival

Treatment

General measures

1- **Discontinuation** of alcohol use and resumption of a nutritious diet
   - The cornerstones of therapy for alcoholic patients even after cirrhosis has developed

2- **Hospitalization** for patients with significant extrahepatic complications of alcoholism
   - Electrolyte abnormalities
   - Cardiac dysfunction
   - Pancreatitis

- Hemorrhagic gastropathy
- Major alcohol withdrawal syndromes
- Infection

Specific therapy

1- **Corticosteroids:**

- Dose: a 4-week course of prednisolone (40 mg/day).
- Trials have demonstrated that patients with clinically severe alcoholic hepatitis benefit from treatment with corticosteroids once serious infection and/or gastrointestinal bleeding have been controlled
- Review found that mortality was decreased with the use of steroids

2- **Pentoxifylline (PTX):**

- It's a nonselective phosphodiesterase inhibitor that is approved (at a dose of 400 mg orally t.i.d.) by the Food and Drug Administration for use as a rheologic agent
- It significantly reduced 4-week mortality to 24.5% from 46.1% (in the placebo group); it also reduced the frequency of hepatorenal syndrome from 34.6% (in placebo) to 8.2%.
- The mechanisms are mediated through modification of cytokines synthesis and/or effect (e.g. TNF).
- It should be included in the list of therapies (with corticosteroids) for the management of acute alcoholic hepatitis

3- **Antioxidants:**

- **S-adenosylmethionine (SAM):**
  - A multicenter clinical study reported that SAM in a daily dose of 1200 mg significantly reduced the mortality rate and decreased the need for liver transplantation in patients with Child's A and B alcoholic cirrhosis.
- **Silymarin:**
  - It has antioxidant properties, protects against lipid peroxidation, and exerts anti-inflammatory and antifibrotic effects.

  - Despite these properties, insufficient data are available to demonstrate improvement in mortality, complications of cirrhosis, or histology in patients with alcoholic liver disease

- **Vitamin E:**
  - Vitamin E deficiency has been well documented in patients with alcoholic liver disease.
  - Vitamin E has hepatoprotective effects in experimental liver injury, with potentially beneficial effects that include membrane stabilization, reduced TNF production, and inhibition of hepatic stellate cell activation and collagen production.
  - Unfortunately, the largest randomized study of vitamin E supplementation in patients with alcoholic liver disease did not show a significant benefit, possibly because a relatively low dose was used

4- Parenteral amino acids:

- Ethanol interferes with intestinal absorption, storage of nutrients and reduces appetite for nonalcoholic sources of calories, this may result in deficiencies of protein, vitamins, & minerals
- Parenteral amino acids have been reported to improve nutritional status, serum bilirubin levels, and aminopyrine breath test results but not to increase the rates of short or long-term survival

5- Other supplements:

- Patients who are actively drinking are generally severely depleted of magnesium, potassium, and phosphate. This can precipitate multi-organ system dysfunction. Therefore, these elements should be repleted promptly
- **Thiamine:** must be administered to prevent Wernicke's encephalopathy

6- Drugs of unlikely benefit:

- Colchicine

- Propylthiouracil
- Ursodeoxycholic Acid

Hepatic encephalopathy

Definition

1- **Overt hepatic encephalopathy (OHE):**
  - Wide spectrum of neurologic and neuropsychiatric abnormalities in patients with significant liver dysfunction

2- **Covert/minimal hepatic encephalopathy (covert HE):**
  - Disorder in which patients with cirrhosis have normal mental and neurologic status on clinical examination but exhibit reversible and quantifiable neuropsychologic and/or neuropsychiatric abnormalities

Classification

1998 Hepatic Encephalopathy Working Party proposed classification of HE

Type	Description	Subcategory	Subdivision

A	Encephalopathy associated with acute liver failure	—	—
B	Encephalopathy with portosystemic bypass and no intrinsic hepatocellular disease	—	—
C	Encephalopathy associated with cirrhosis or portal HTN/portosystemic shunts	Episodic	* Precipitated * Spontaneous * Recurrent
		Resistant	* Mild * Severe * Treatment dependent
		Covert	------

Stages of hepatic encephalopathy

Stage	Description
1	Mild confusion, agitation, irritability, sleep disturbances and ↓ attention
11	Lethargy, disorientation, inappropriate behaviour and drowsiness
111	Somnolent but arousable, slurred speech, confused and aggressive
1v	Coma

Clinical features [presentation]

1- **Acute liver failure**–associated encephalopathy

2- **Covert HE:**

- Patients with normal neurologic examination but abnormal neuropsychiatric test performance

3- **Single or recurrent HE**

- Two episodes of HE within 1 year

4- **Persistent HE**

- Low-grade HE (covert HE + grade I HE): mental status changes without disorientation
- High-grade HE (stage II to IV): mental status changes with disorientation

5- **Chronic portosystemic encephalopathy:**

- Acquired hepatocerebral degeneration
- Spastic paraparesis

  These 2 conditions are very rare and resulting from fluctuating HE + major long standing spontaneous shunting in patients with portal HTN and also exception to the rule that HE is usually reversible

Diagnosis

1- **The key to diagnosis of HE is recognition that significant liver disease is present:**
   - Clinical or laboratory evidence of liver failure and/or portal HTN is usually obvious
   - In a minority of patients, evidence of significant liver dysfunction may be subtle, as in the following conditions:
     - Well-compensated cirrhosis (e.g., chronic hepatitis C, remote alcohol abuse)
     - Noncirrhotic portal HTN (Splanchnic vein thrombosis, Schistosomiasis, Noncirrhotic portal fibrosis and Idiopathic portal hypertension)
     - Congenital hepatic fibrosis
     - Congenital intrahepatic and extrahepatic portosystemic shunts

2- **Historical points suggesting occult liver disease and/or portosystemic shunting**
   - Past history of injection drug use
   - Family history of cirrhosis (hemochromatosis)
   - Residence in areas endemic for schistosomiasis
   - Umbilical sepsis (splanchnic vein thrombosis)
   - History of pancreatitis (splenic vein thrombosis)
   - Past history of hepatitis (hepatitis B or C, alcoholic hepatitis)
   - Past history of hepatotoxic drugs (e.g., methotrexate, nitrofurantoin)

3- **Physical signs suggesting underlying significant liver disease**
   - Upper extremity
     - Clubbing, leukonychia
     - Dupuytren’s contracture, palmar erythema

- Spider telangiectasias, tattoos, injection marks, asterixis
- Scratch marks, pigmentation, ecchymoses
- Loss of muscle mass

- Eyes and face
  - Conjunctival icterus, cyanosis, parotid enlargement
  - Kayser–Fleischer rings
- Chest
  - Spider telangiectasias, loss of axillary hair, gynecomastia
- Abdomen
  - Splenomegaly (usually < 5 cm below costal margin)
  - Hepatomegaly
  - Caput medusa
  - Ascites
- Testicular atrophy
- Loss of escutcheon
- Loss of hair on the shins
- Pedal edema

4- Laboratory test abnormalities

- Hepatic synthetic dysfunction: ↑ PT, ↓ serum albumin
- ↑ ammonia levels (not routinely recommended)
- Hypergammaglobulinemia
- Pancytopenia, leukopenia, thrombocytopenia
- ↑ CSF glutamine levels
- ↓ plasma branched chain/aromatic amino acid ratio
- Hepatitis C antibody–positive status
- Hepatitis B surface antigen–positive status

The foregoing historical points, physical signs, and laboratory tests can individually or in combination indicate the presence of underlying liver dysfunction even when results of traditional tests of hepatic function, as serum albumin and PT, are normal

Patients with well-preserved synthetic function of the liver do not commonly develop overt HE; a major precipitating factor is needed to induce an episode in such patients

Treatment

1- **Response to treatment** confirms the diagnosis of HE post hoc

2- **Four-pronged strategy for acute treatment**

- General supportive care of the unconscious patient
- Exclusion of other causes of encephalopathy and treatment of any present
- Identification and treatment of correctable precipitating factors
- Initiation of empirical treatment

3- **Exclusion of other causes of encephalopathy**

- Patients with significant liver dysfunction are susceptible to many causes of encephalopathy other than HE:
  - Sepsis
  - Hypoxia
  - Hypercapnia
  - Acidosis
  - Uremia
  - Sensitivity to CNS drugs
  - Gross electrolyte changes
  - Postictal confusion
  - Delirium tremens
  - Wernicke–Korsakoff syndrome
  - Intracerebral hemorrhage
  - CNS sepsis
  - Pancreatic encephalopathy
  - Drug intoxication
  - Cerebral edema/intracranial hypertension (usually seen in acute liver failure)
  - Hypoglycemia (usually seen in acute liver failure)
- Many patients simultaneously have other causes of encephalopathy as well as HE, a situation contributing to difficulty in diagnosing HE

4- **Identification of precipitating factors**

- Most patients with significant liver disease (except for type A HE) have an identifiable precipitating factor responsible for inducing the onset of an episode of HE
- Some precipitating factors can enhance the production and/or absorption of gut compounds
- Correcting these conditions is a key aspect of the treatment of HE
- Other precipitating factors are less obvious but may act by reducing hepatic function
- Sepsis and CNS-active drugs can independently cause encephalopathy or precipitate HE
    - Sepsis
    - Gastrointestinal hemorrhage (Shock → ↓ hepatic perfusion & Protein load → ↑ metabolites)
    - Constipation
    - Dehydration
    - Aspiration of ascites
    - Hypokalemia/alkalosis
    - Excessive diuretics (Hypovolemia & Hypokalemic alkalosis)
    - Dietary protein overload
    - SBP or any infection
    - Postanesthesia status
    - Bowel obstruction or ileus
    - Superimposed hepatic injury
    - CNS-active drugs
    - Poor compliance with lactulose therapy
    - Postportal decompression procedure
    - Uremia
    - Development of HCC

5- **Empiric therapy**

- Gut cleansing with enemas (every 8 hr or when needed) and gastric aspiration or lavage
- Low-protein or zero-protein diet
    - Stage 1 or 11 HE: ↓ to 0.5 – 1.5 gm/kg/day
    - Stage 111 or 1v HE: transient ↓ to 0.5 gm/kg/day
    - Then ↑ protein to the limit of tolerance as HE improves

- Delivery of lactulose:
  - It is a non absorbable disaccharide (osmotic purgative): wash the bowel from nitrogenous substances
  - Action:

    © Conversion to lactic acid and acetic acid resulting in acidification of the gut lumen. This favors conversion of ammonia (NH_3) to ammonium (NH_4^+), which is relatively membrane impermeable; therefore, less ammonia is absorbed by the colon

    © Gut acidification inhibits ammoniagenic coliform bacteria, leading to increased levels of nonammoniagenic lactobacilli

    © Work as a cathartic, clearing the gut of ammonia before it can be absorbed
  - 15 mL orally or by NGT every 2 hours until loose bowel movements initiated
  - Then 30 mL orally 2-3 times daily to do 2-3 bowel movements per day
  - Lower doses may suffice if the patient is not comatose
  - Higher doses are not more efficacious, and overtreatment can cause dehydration and electrolyte abnormalities that can result in worsening of HE
  - For patients at risk of aspiration (coma), lactulose can be administered as an enema (300ml in 700 ml of water, retained for one hour in the Trendelenburg position) every 2-4 hours as needed until mental function improves
  - Side effects of recommended doses include: diarrhea and flatulence and abdominal cramps
- Empiric therapy may be effective by correcting precipitating factors; however, because no way of predicting the response to correcting precipitating factors exists, all patients should receive full empiric therapy
- Cefotaxime: to eradicate any infection esp. SBP

- Avoid sedatives: but if absolutely necessary if the patient is violent, give small dose of short acting benzodiazepine e.g. midazolam (dormicum) with flumazinel is ready as an antidote

6- **Treatment response**

- In all cases of OHE in chronic liver disease, it should be possible to reverse encephalopathy
- Failure to reverse HE after 72 hours of treatment may indicate the following:
  - Another cause of encephalopathy has been missed or treated inadequately
  - A precipitating factor has been missed or treated inadequately or remains uncorrected
  - Effective empirical therapy has not been instituted
  - Excessive lactulose therapy has induced dehydration
- The most common reason for ineffective therapy is lack of delivery of lactulose into the small intestine or right colon. Only intestinal obstruction or ileus should prevent adequate delivery
- Reluctance to use nasogastric tube delivery of lactulose in the comatose patient because of fear of precipitating variceal bleeding is unwarranted

7- **Second-line therapy if needed**

- Rifaximin: 550 mg orally twice daily (unabsorbed and well tolerated for long time)
- Metronidazole: 250 mg orally 4 times daily (recommend only short term) esp. with renal impairment
- Neomycin: 500 mg orally 4 times daily (use higher doses with caution), poorly absorbed and may cause nephrotoxicity and ototoxicity (recently not used)
- Vancomycin: 250 mg orally 4 times daily
- Sodium benzoate (not approved for use in the United States)

- Flumazenil (may be effective but very short duration of action)

8- **Problems peculiar to type A HE**

- Type A accounts for small fraction of HE cases per year
- Treatment follows the same principles as in chronic liver disease, except for the following:
    - Precipitating factors not obvious, and, even if present, correction is usually not effective
    - Overall response to empiric therapy is poor
    - If deep coma occurs, the prognosis is poor without liver transplantation
    - Cerebral edema and intracranial HTN are common and often lethal
    - Other concurrent causes of encephalopathy are common (e.g., hypoglycemia, acidosis, sepsis)
    - Approximately 20% of patients have an agitated delirium or seizure phase

9- **Long-term treatment**

- Lactulose
- Rifaximin
- Vegetable-based protein
- Diet enriched with branched-chain amino acids
- Bromocriptine or L-dopa: improves cerebral neurotransmission
- Zinc repletion: (600mg/day) → improve hyperammonemia by increasing the activity of ornithine transcarbamylase, an enzyme in the urea cycle. The subsequent increase in ureagenesis results in the loss of ammonia ions
- Sodium benzoate
- Ornithine aspartate (hepamerz): ↓ blood NH3

10-**The foregoing therapies** are usually used for maintenance treatment. Failure of one generally leads to trying the next listed treatment. A long-term low-protein diet is not ideal because protein restriction to avoid HE does not allow maintenance of nitrogen balance

11- **Options for intractable or recurrent HE**

- Liver transplantation
    - Treatment for intractable HE

        - Treatment for recurrent HE or HE responsive only to a low-protein diet

- Modification of existing portosystemic shunts
    - Surgical shunts or TIPS may be amenable to closure, possibly in combination with other measures to prevent recurrent variceal bleeding or reduction in shunt diameter
    - The foregoing can be achieved in selected cases by radiologic and/or surgical intervention, which is usually attempted only if the patient is not a liver transplant candidate
    - Acquired spontaneous portosystemic shunts are occasionally amenable to occlusion (by embolization) or reduction in flow (e.g., splenic artery embolization).
    - Congenital portosystemic shunts are amenable to closure in some cases
- Other options
    - Colonic exclusion: virtually abandoned
    - Arterialization or portal venous stump: abandoned
    - Radiologic portal vein thrombolysis plus TIPS
    - TIPS in Budd–Chiari syndrome

Surgery in the hepatic patient

Effects of anesthesia and surgery on the liver

Overview

1- **Surgical procedures** using general or local (i.e., spinal or epidural) anesthesia
    - Often followed by changes in liver biochemical test results

2- **Postoperative elevations** of serum aminotransferase, alkaline phosphatase, or bilirubin levels are
    - Generally minor and transient
    - Not clinically significant in patients without underlying cirrhosis

3- **Clinically significant hepatic dysfunction:**
    - Can occur in patients with preexisting acute liver disease or cirrhosis
    - More common in patients with compromised hepatic synthetic function

Effects of anesthetic agents on the cirrhotic liver

1- **At baseline**, hepatic arterial and venous perfusion of the cirrhotic liver is decreased because of the following:
    - Portal hypertension that decreases portal blood flow
    - Impaired autoregulation that decreases arterial blood flow
    - Arteriovenous shunting around the liver
    - Reduced splanchnic inflow

2- **Sequlae:**
    - Decreased hepatic perfusion at baseline makes the cirrhotic liver more susceptible to hypoxemia and hypotension in the operating room
    - Induction causes a reduction in hepatic blood flow by 30% - 50%.

Other intraoperative factors

[May decrease hepatic oxygenation by further ↓ hepatic blood flow or ↑ splanchnic vascular resistance]

1- **H**ypotension caused by hepatorenal syndrome or shock

2- **H**emorrhage

3- **H**ypoxemia caused by ascites, hepatic hydrothorax, hepatopulmonary syndrome, portopulmonary hypertension, or aspiration

4- **H**ypercapnia

5- **H**eart failure

6- **Vasoactive drugs**

7- Intermittent positive **pressure** ventilation

8- **Pneumoperitoneum** during laparoscopic surgery

9- **Traction** on abdominal viscera: reflex dilatation of splanchnic capacitance vessels

Hepatic metabolism of anesthetic agents

1- **Inhalational anesthetic agents** are lipid-soluble compounds that require hepatic transformation to more water-soluble compounds for biliary excretion

2- **Consequences of hepatic metabolism:**

- Prolonged anesthetic action in patients with liver disease (also caused by hypoalbuminemia and impaired biliary excretion)
- Formation of toxic intermediates or reactive oxygen species, especially in the presence of hypoxia or reduced hepatic blood flow
  - Halothane → hepatitis (rare)
  - Enflurane → hepatitis (even rarer)

3- **Drugs preferable with liver disease:**

- Isoflurane, desflurane, sevoflurane, and nitrous oxide
- These agents undergo the least hepatic metabolism and hepatic arterial blood flow alterations, and resulting hepatitis is rare

4- **Propofol:**

- Is an excellent anesthetic choice in patients with liver disease
- Although it is metabolized by hepatic glucuronidation, its serum half-life remains short even in patients with cirrhosis, and it does not precipitate hepatic encephalopathy

Other agents in liver disease

1- **Narcotics and sedatives** are generally well tolerated in patients with compensated liver disease

- These drugs have a prolonged duration of action in decompensated liver disease

- Narcotics have high first-pass extraction by the liver:

© Blood levels increase as hepatic blood flow decreases
© Bioavailability is increased because of portosystemic shunting
© Preferred agents are fentanyl and sufentanil, which have similar durations of action in healthy persons and in patients with cirrhosis

- Benzodiazepines have low first-pass extraction by the liver:

© Those eliminated by glucuronidation (oxazepam, lorazepam) are not affected by liver disease
© Those not glucuronidated (diazepam, chlordiazepoxide) have enhanced sedative effects in liver disease and should be avoided

- They may precipitate hepatic encephalopathy in patients with severe liver disease
- Smaller than standard doses are indicated for those drugs whose metabolism is affected by liver disease

2- **Muscle relaxants**

- Succinylcholine should be avoided:
    - Resistance occurs in patients with liver disease in part because of decreased hepatic pseudocholinesterase production.
    - The large doses required in patients with liver disease may cause difficulty in reversing their effect postoperatively
- Nondepolarizing muscle relaxants:
    - The volume of distribution is increased.So, larger doses may be required
    - Atracurium and cisatracurium are preferred because neither the liver nor the kidney is required for elimination
    - Doxacurium is preferred for longer cases such as liver transplantation and is metabolized by the kidney

Effect of surgery

1- **The nature and extent of surgery** may be more important determinants of postoperative hepatic dysfunction than anesthesia

2- **Perioperative risk** :

  - Increased with biliary tract and open abdominal surgery
  - Greatest with cardiac surgery and liver resection
  - In patients with cholecystitis:
    - Laparoscopic cholecystectomy is permissible in patients in Child-Pugh class A and selected patients in Child-Pugh class B without portal hypertension
    - However, in patients with more advanced cirrhosis with portal hypertension, cholecystostomy is preferable
  - Risk factors for hepatic decompensation after cardiac surgery include:
    - Total time on cardiopulmonary bypass support (cardiopulmonary bypass may exacerbate coagulopathy)
    - Use of pulsatile as opposed to nonpulsatile bypass
    - Need for perioperative vasopressor
  - Less invasive cardiovascular procedures (e.g., angioplasty, valvuloplasty, endovascular aneurysm repair) are preferred to open surgery in patients with advanced cirrhosis.
  - Occasionally, however, major cardiac surgery (including heart transplantation) may be performed at the same time as liver transplantation

Estimation of operative risk in patients with liver disease

Absolute contraindications to elective surgery in patients with liver disease [other than liver transplantation]

Contraindications to elective surgery in hepatic patient
1- Acute liver failure 2- Acute viral hepatitis 3- Alcoholic hepatitis 4- Acute renal failure 5- Severe cardiomyopathy 6- Hypoxemia 7- Severe coagulopathy (despite treatment) 8- American Society of Anesthesiologists class V

Problems in estimating operative risk

1- Large prospective studies and randomized controlled trials are lacking
2- Data on acute and chronic hepatitis are limited
3- The effects of comorbid conditions on surgical risk are difficult to quantitate

Acute hepatitis

1- Acute hepatitis of any cause **increases operative risk**
2- Elective surgery can usually be **avoided** in patients with acute hepatitis.
3- Elective surgery can be undertaken when the patient **improves**

Chronic hepatitis

1- Surgical risk appears to correlate with clinical, biochemical, and histologic severity of disease

- Elective surgery is contraindicated in active, symptomatic disease, particularly when synthetic or excretory function is impaired or portal hypertension is present
- Surgery in patients with autoimmune hepatitis who are receiving corticosteroid therapy requires “stress” doses

2- Hepatitis B or C virus carrier

- These patients have no increased surgical risk.

- In general, antiviral therapy should not be interrupted in the perioperative period
- A risk exists that the patient may infect medical and surgical personnel (the higher the viral load, the higher the risk). Control measures include the following:
  - Universal precautions should be used when contacting any bodily fluid
  - Hepatitis B vaccine should be administered to all personnel at risk
  - Immediate hepatitis B immune globulin and the vaccine series should be given to unvaccinated personnel who sustain an exposure to hepatitis B
  - No postexposure prophylaxis is recommended for hepatitis C

Alcoholic and NAFL disease

1- **Alcoholic fatty liver**
   - Elective surgery is not contraindicated in the presence of normal liver function
   - It may be desirable to postpone surgery until nutritional deficiencies are corrected or the acute effects of alcohol have resolved

2- **Alcoholic hepatitis**
   - A spectrum of severity exists, but surgical risk is increased
   - Severe alcoholic hepatitis is a contraindication to elective surgery
   - Abstinence from alcohol and supportive therapy for at least 12 weeks are generally required before elective surgery

3- **Alcoholism** is associated with additional perioperative risks independent of liver disease:
   - Drug metabolism is altered (e.g., acetaminophen toxicity may occur after standard doses in alcoholic patients)
   - Patients should be observed for signs and symptoms of withdrawal

4- **Nonalcoholic fatty liver disease (NAFLD)**

- At the time of bariatric surgery, approximately 3% of patients are found incidentally to have cirrhosis
- Hepatic steatosis of > 30% may increase mortality and morbidity after major hepatic resection
- Bariatric surgery is not contraindicated in patients with compensated cirrhosis; however, clinically significant portal hypertension increases surgical risk
- NAFLD improves after bariatric surgery in > 90% of cases

Cirrhosis

1- **Cirrhosis is** a pathologic diagnosis characterized by nodular regeneration and vascular distortion leading to portal hypertension

2- **Decompensated cirrhosis** is a clinical diagnosis characterized by the presence of one or more of the following:
   - Ascites
   - Hepatic encephalopathy
   - Varices
   - Hepatorenal syndrome
   - Synthetic dysfunction (hypoalbuminemia or prolonged PT)

3- **Difficulties in detection or diagnosis:**
   - Multiple causes
   - Wide spectrum of severity
   - Lack of correlation between the presence of cirrhosis and biochemical tests of liver function
   - Importance of careful history and physical examination (e.g., cutaneous spiders, palmar erythema, splenomegaly)

4- **Important consequences in the postoperative period:**
   - Fluid and electrolyte disturbances, renal failure
   - Hypoxemia (right-to-left shunts)
   - Altered drug metabolism
   - Increased susceptibility to infection (abdominal abscess, sepsis)

- Nutritional wasting
- Portal hypertension (ascites, variceal hemorrhage)
- Hepatic encephalopathy

Use of Child Pugh classification to assess surgical risk

Risk factors for surgery in patients with cirrhosis [nonportosystemic shunt surgery]

Patient characteristics	- Anemia - Ascites - Child-Pugh class B and C - Encephalopathy - Hypoalbuminemia - Hypoxemia - Infection - Malnutrition - Higher MELD score - Portal hypertension - postoperative bleeding - Prolonged INR >1.5 that does not correct with vitamin K - Prolonged PT, PTT - Elevated serum bilirubin - Higher American Society of Anesthesiologist class
Type of surgery	- Cardiac surgery - Emergency surgery - Hepatic resection - Open abdominal surgery esp. biliary

1- **Child-Pugh classification reliably predicted** operative mortality in independent studies over a 27-year span:
   - Child-Pugh class A mortality: 10%
   - Child-Pugh class B mortality: 17 - 30%
   - Child-Pugh class C mortality: 63% - 82%

2- **Problems with the use of the Child-Pugh classification:**
   - Definition of terms (e.g., “no ascites” means clinically or sonographically absent?)
   - Subjective parameters (e.g., encephalopathy: “mild” versus “advanced”)

  - Assignment of overall class based on components in different classes (Child–Turcotte– Pugh score uses point system to add greater precision)

3- **Child-Pugh classification** has been the most widely used predictor of surgical risk.

4- **It correlates with** postoperative mortality and morbidity:

  - Liver failure
  - Encephalopathy
  - Bleeding
  - Sepsis
  - Ascites
  - Renal failure
  - Pulmonary failure

5- **When using the Child-Pugh classification**, additional risk factors predictive of perioperative mortality include the following:

  - Emergency surgery
  - Biliary tract surgery: marked vascularity of the gallbladder bed in patients with portal hypertension
  - Hepatic resection: generally contraindicated in decompensated cirrhosis but feasible in Child-Pugh class A cirrhosis (risk of morbidity and mortality correlates with preoperative portal hypertension and the amount of liver resected)
  - Additional risk factors for hepatic resection: active hepatitis, thoracotomy, pulmonary disease, diabetes mellitus, malignancy, and fatty liver
  - Cardiac surgery
  - Hypoxemia ($Po2 < 60$ mm Hg): e.g., as a result of hepatopulmonary syndrome or portopulmonary hypertension
  - Risk of surgery on the respiratory tract: increased in patients with chronic obstructive pulmonary disease and cirrhosis
  - Ascites: risk of abdominal wall herniation and wound dehiscence

Use of the MELD score to assess surgical risk

1- **Uses:**

- The MELD score was developed to predict outcomes following insertion of a TIPS
- It is used to prioritize candidates for liver transplantation
- Increasingly used to predict surgical risk in patients with cirrhosis.

2- **Advantages of MELD score** over the Child-Pugh classification:

- Objective
- Weighs the variables
- Does not rely on arbitrary cutoff values
- The result is increased precision in predicting postoperative mortality

3- **Results of the largest retrospective study** of MELD as a predictor of perioperative mortality are as follows:

- MELD score up to 7: Mortality rate was 5.7%.
- MELD score of 8 - 11: Mortality rate was 10.3%.
- MELD score of 12 - 15: Mortality rate was 25.4%.
- The increase in risk of death was almost linear for MELD scores higher than 8
- Limitations:
    - Median MELD score was 8; few patients had a MELD score > 15
    - Most patients had a platelet count > 60,000/mm3 and an INR < 1.5

4- **When using the MELD score** to predict surgical risk, additional risk factors predictive of perioperative mortality include the following:

- ASA class
    - In ASA class IV, patients add 5.5 MELD points
    - ASA class V is a contraindication to surgery, except liver transplantation; 100% mortality is expected
- Older age; in patients whose age is more than 70 years, add 3 MELD points

5- **To calculate 7-day, 30-day, 90-day, and 1-year surgical mortality** based on the MELD score, ASA class, and age, use the algorithm at http://www.mayoclinic.org/meld/mayomodel9.html

6- **In patients with a MELD score ≥15**

- A serum albumin level ≤ 2.5 mg/dL has been shown to be associated with a much higher postoperative mortality rate (60%) than that associated with a serum albumin level >2.5 mg/dL (14%).

American Society of Anesthesiologists classification

Class	Characters
I	Healthy patient
II	Patient with mild systemic disease without functional limitation
III	Patient with severe systemic disease with functional limitation
IV	Patient with severe systemic disease that is a constant threat to life
V	Moribund patient not expected to survive >24 hr with or without surgery
E	Emergency nature of surgery (added to classification I–V above)

Obstructive Jaundice

Surgical risk

1- **Mortality rate:** 8% to 28%

2- **Risk factors based on a multivariate analysis** performed in 373 patients undergoing surgery for relief of biliary obstruction:

- Initial hematocrit value < 30%
- Initial serum bilirubin level > 11 mg/dL
- Malignant cause of obstruction
  - All three present → mortality rate 60%
  - All three absent → mortality rate less than 5%

3- **Additional risk factors** for morbidity and mortality after surgery for obstructive jaundice:

- Azotemia
- Hypoalbuminemia
- Cholangitis

4- **Risk factors for surgery of bile duct stones:**

- Serum bilirubin level
- Other medical illnesses (however, not a risk factor for endoscopic sphincterotomy)
- Preoperative endoscopic sphincterotomy

5- **Situations in which endoscopic sphincterotomy** for bile duct stones is preferable to surgery:

- Patients at high operative risk
- Retained stones after cholecystectomy
- Severe acute cholangitis

Perioperative complications

1- **Renal failure**

- Decreased glomerular filtration rate in 60% - 75% (versus less than 1% of anicteric surgical patients)
- Frank renal failure in 8% with a mortality rate > 50%

2- **Disseminated intravascular coagulation**

3- **Gastric stress ulcers and bleeding**

4- **Delayed wound healing**, wound dehiscence, and incisional hernias

5- **Strategies to reduce potential complications:**

- Reduction or prevention of endotoxemia: experimental—oral bile salts, oral antibiotics, or lactulose
- Preoperative intravenous antibiotic administration to prevent wound infection
- Adequate perioperative hydration: possibly a critical factor
- Avoidance of aminoglycosides and NSAIDs because these drugs may precipitate renal failure

These complications are presumed to result from increased circulating levels of endotoxin caused by impaired bile salt delivery to bowel and decreased hepatic reticuloendothelial function

Preoperative biliary decompression

1- **Endoscopic or percutaneous biliary drainage** is preferable to surgery for **benign** conditions in cirrhotic patients
   - Sphincterotomy is associated with an increased risk of bleeding in patients with coagulopathy or thrombocytopenia; in these patients, balloon dilatation is preferable

2- **Routine biliary decompression before surgery for malignant obstruction**
   - Does not reduce subsequent operative mortality and increases morbidity
   - Complications of transhepatic biliary drainage include:
     - Cholangitis
     - Sepsis
     - Dehydration
     - Catheter displacement
   - Routine preoperative endoscopic internal biliary drainage :
     - Increases the rate of morbidity and does not decrease the rate of mortality in patients undergoing pancreatic cancer resection
     - Therefore, not recommended unless surgery is delayed and the patient has cholangitis or pruritus

3- **Endoscopic biliary decompression:**
   - Is a useful alternative to surgery for palliation of patients with inoperable malignancy or poor surgical risk; however, it does not generally prolong survival.
   - Endoprosthesis insertion may also be a reasonable alternative to operative bypass in selected patients; endoscopic stenting is associated with fewer early complications and surgery with fewer late complications

Hepatic resection

1- **MELD is the best predictor** of morbidity and mortality in patients with cirrhosis who undergo liver resection
    - In a large study of 1017 patients, a MELD score higher than 8 was associated with a mortality rate of 4% and a morbidity rate of 16%, although most patients underwent small resections and had a mean MELD score of 6
    - In another study, the postoperative mortality rate for patients with a MELD score of 9 or higher was 29% versus 0% for those with a MELD score lower than 9

2- **Alternatives to hepatic resection** in patients with HCC include:
    - Radiofrequency ablation
    - Percutaneous ethanol injection
    - Transarterial chemoembolization
    - Doxorubicin- or yttrium-90–impregnated microsphere embolization
    - External beam radiation with CyberKnife
    - Liver transplantation

3- **Postresection liver failure is defined by the "50-50" rule:**
    - The PT index (patient's PT relative to control PT) < 50% (the INR is > 1.7).
    - The serum bilirubin level is > 50 µmol/L (2.9 mg/dL).
    - The mortality rate is 59% when these criteria are met versus 1.2% when they are not met

Preoperative Evaluation and Preparation

General measures

1- **History and physical examination:**

- Patients should be screened for unrecognized liver disease (routine liver biochemical tests in asymptomatic healthy patients are not required).
- Patients with cirrhosis can have normal laboratory test results; screening laboratory testing cannot replace a through history and physical examination
- The status of patients with known liver disease should be assessed (determine Child-Pugh class, MELD score, ASA class)
- A careful medication and alcohol history should be included
- Physical examination findings in cirrhosis may include palmar erythema, spider angiomas, abnormal hepatic size or contour, splenomegaly, hepatic encephalopathy, ascites, testicular atrophy, and gynecomastia

2- **Liver biochemical tests** [AST,ALT, ALP, bilirubin, and albumin]:

- Of unclear cost effectiveness in healthy, asymptomatic patients
- Indicated in:
    - Patients who drink alcohol regularly
    - Those with a remote history of hepatitis or risk factors for hepatitis (e.g., injection drug use)
    - Check hepatitis B surface antigen and antibody to hepatitis C virus
- Further investigation of any patient with clinical or biochemical evidence of liver disease:
    - Hepatocellular dysfunction: biochemical and serologic testing for viral hepatitis, autoimmune liver disease, and metabolic disorders; possible liver biopsy
    - Cholestasis: radiologic or endoscopic imaging (abdominal ultrasonography, possibly magnetic resonance, endoscopic, or transhepatic cholangiography), with or without liver biopsy

Treatment of coagulopathy

1- Impaired hemostasis in liver disease

- Vitamin K deficiency: decreased levels of factors II, VII, IX, and X
- Decreased hepatic protein synthesis: decrease in levels of all factors except VIII, which may be increased
- Low-grade DIC causing increased fibrinolysis
- Pattern of hemostatic abnormalities:
    - Prolonged PT
    - Normal or increased PTT
    - Prolonged thrombin time
    - Low plasma fibrinogen level
    - Decreased plasma levels of antithrombin, protein C, and protein S
- Thrombocytopenia: result of :
    - Hypersplenism
    - Alcohol-induced bone marrow suppression
- The degree of prolongation of the PT does not correlate with the patient's risk of bleeding because of changes in levels of both procoagulant and anticoagulant factors in the plasma of patients with cirrhosis

2- Preoperative preparation

- Vitamin K 10 mg intravenously (one to three doses): corrects hypoprothrombinemia related to malnutrition or intestinal bile salt deficiency, not hepatocellular disease
- Fresh frozen plasma in patients with hepatocellular dysfunction: aim for an INR lower than 1.5 (large volumes, short half-life limit efficacy)
- Platelet transfusions: 8 - 10 U when count is lower than 50,000/mm3
- Surgical risk and bleeding risk in patients with INR > 1.5 or platelets < 50,000/mm3 are unknown because they have not been studied
- Adjunctive therapy considered only when active bleeding does not respond to standard measures:
    - 1-deamino-8-d-arginine vasopressin (DDAVP, factor VIII stimulant, shortens bleeding time, clinical usefulness uncertain)

- Antifibrinolytic agents (ε-aminocaproic acid, tranexamic acid, value uncertain)
- Recombinant factor VIIa (expensive, short half-life, of unproven benefit)

Treatment of ascites

1- **Derangements in liver disease**

- Factors contributing to development of ascites with or without hepatic hydrothorax in cirrhosis:
    - Portal hypertension
    - Decreased plasma oncotic pressure (hypoalbuminemia)
    - Increased hepatic lymph
    - Secondary hyperaldosteronism
    - Peripheral vasodilatation → stimulation of renin-angiotensin system → renal vasoconstriction → avid sodium retention
- Associated electrolyte abnormalities:
    - Hyponatremia (impaired free water clearance)
    - Hypokalemic alkalosis

2- **Management**

- Diagnostic paracentesis in patients with new or worsening ascites:
    - To exclude infection or malignancy
    - And to differentiate spontaneous from secondary (surgical) bacterial peritonitis
- Control of ascites before abdominal surgery to reduce risk of postoperative wound dehiscence or herniation:
    - Rigid salt restriction (2-g sodium diet)
    - Combination diuretics: spironolactone 100 → 400 mg/day + furosemide 40 → 160 mg/day, if necessary
    - Preoperative TIPS: may lower surgical risk in patients with low MELD scores, no encephalopathy, and refractory ascites or large varices who require intra-abdominal surgery

  - Monitoring of patient's weight, intake and output, urinary sodium concentration (greater than 25 mEq/L if diuretics are effective); if necessary, central venous pressure monitoring
  - 1L fluid restriction if hyponatremia (sodium lower than 125 mEq/L) present
- When intraoperative volume expansion is needed:
  - Blood products, intravenous 25% saltpoor albumin, and (in the absence of hyponatremia) 5% dextrose in water (D5W) can be administered
  - Crystalloid should be avoided if possible

Treatment of renal dysfunction

1- **Decompensated cirrhosis leads** to increased levels of endogenous vasodilators, peripheral vasodilatation, chronic hyperdynamic circulation, and low blood pressure
   - Serum creatinine may overestimate renal function because of muscle wasting and decreased urea synthesis
   - Serum creatinine and blood urea nitrogen (BUN) should be monitored perioperatively

2- **The following nephrotoxic drugs** should be avoided:
   - Aminoglycosides
   - Nonsteroidal anti-inflammatory drugs
   - Intravenous contrast agents

3- **The differential diagnosis of acute kidney injury** in patients with cirrhosis includes the following:
   - Volume depletion
   - Drug nephrotoxicity
   - Acute tubular necrosis
   - Hepatorenal syndrome

4- **Hepatorenal syndrome**
   - Characterized by :

    - Serum creatinine level >1.5 mg/dL
    - Despite diuretic withdrawal and volume expansion with intravenous salt-poor albumin
    - In the setting of cirrhosis and ascites
    - And the absence of parenchymal kidney disease and nephrotoxic drug use
- It may be precipitated by :
    - Sudden volume loss (e.g., bleeding, rapid diuresis, paracentesis)
    - Infection (e.g., spontaneous bacterial peritonitis)
    - Or a decrease in cardiac output
- Potential treatments are as follows:
    - Oral midodrine (an alpha agonist), subcutaneous octreotide, and intravenous albumin (not approved by FDA)
    - Intravenous norepinephrine (titrated to increase mean arterial pressure 10 mm Hg) and intravenous albumin (not approved by FDA for this indication)
    - Intravenous terlipressin (under study but not available in the United States) and intravenous salt-poor albumin

Treatment of hepatic encephalopathy

1- **Pathophysiology**: This state of disordered central nervous system function is characterized by disturbances in consciousness, behavior, and personality. Pathogenic factors include the following:

- Shunting of portal venous blood into the systemic circulation
- Hepatic dysfunction resulting in failure to detoxify neurotoxic agents such as ammonia

2- Diagnosis

- Obvious in patients with confusion or stupor, asterixis, and elevated blood ammonia level
- Possibly subtle:
    - Sleep disturbances such as day-night reversal

    - Personality changes
    - Tremor
    - Hyperreflexia
- Importance of preoperative recognition: high frequency in the postoperative period of precipitating or exacerbating factors:
    - Gastrointestinal bleeding
    - Constipation
    - Azotemia
    - Hypokalemic alkalosis
    - Sepsis
    - Hypoxia
    - Use of central nervous system depressant drugs (e.g., narcotics or benzodiazepines)

3- **Treatment**

- Control of clinically overt encephalopathy preoperatively (preemptive therapy is of unproven benefit)
- Correction of precipitating factors
- Lactulose: oral unabsorbable disaccharide in dose needed to achieve three bowel movements per day:
    - Converts intestinal ammonia (NH_3) to unabsorbable ammonium (NH_4^+)
    - Enhances growth of nonammoniagenic intestinal bacteria
- Oral antibiotics should be added when lactulose has not achieved adequate control (e.g., rifaximin 550 mg twice daily)

Miscellaneous issues

1- **Risk of hypoglycemia** in acute hepatic failure and to a lesser extent in cirrhosis:

- When this risk is present, an intravenous infusion of 10% dextrose in water (D10W) should be administered

2- **Gastroesophageal varices:**

- Primary prophylaxis with nonselective beta blockers or endoscopic band ligation to prevent variceal bleeding is indicated

3- All cirrhotic patients are at high risk of **protein-energy malnutrition**

- Mortality is increased after surgery in malnourished patients
- When time permits, preoperative enteral nutritional supplementation improves immunocompetence and short-term prognosis
- Percutaneous gastrostomy is contraindicated in patients with ascites or coagulopathy

Postoperative monitoring for signs of hepatic decompensation

1- Clinical: onset of

- Jaundice
- Encephalopathy
- Ascites

2- Laboratory:

- Rise in serum bilirubin
- Prolongation of PT
- Worsening renal function
- Hypoglycemia

Post-operative jaundice

Definition

The presence of **bilirubin elevation** ± clinical icterus appearing in the period following surgery, and can occur in patients with or without underlying liver disease

Incidence

1- Incidence of Postoperative hepatic dysfunction **1%** (mild jaundice to hepatic failure)

2- Incidence of abnormal postoperative liver function tests (LFT's) **25 – 75%**

3- **47%** of cirrhotic patients develop jaundice after general anaesthesia

Causes

1- **Increased bilirubin load = [prehepatic]**

- Hemolysis after transfusion
- Hematoma resorption or hemoperitoneum
- Underlying hemolytic anemia
- Gilbert's syndrome
- Post cardiac surgery status

2- **Impaired hepatocellular function = [intrahepatic]**

■ Due to injury to hepatocytes or biliary epithelial cells

■ Clinicaly more severe in patients with preexisting liver disease

- Anesthesia drugs:
  - Halothane, enflurane
  - Rarely isoflurane, desflurane, sevoflurane
- Other drugs: e.g.,
  - Phenothiazines
  - Isoniazid
  - Methyldopa
  - Androgens
  - Estrogens
  - Phenytoin
- Antibiotics:
  - Tetracycline
  - Chloramphenicol
  - Erythromycins
  - Sulfonamides
  - Nitrofurantoin
  - Augmentin
- Total parenteral nutrition
- Viral hepatitis
- Ischemic hepatitis
- Sepsis

- Benign postoperative intrahepatic cholestasis

3-**Extrahepatic obstruction = [post hepatic]**

- Bile duct stone
- Cholecystitis, cholangitis, abscesses
- Biliary stricture, leak, tumor
- Pancreatitis

Approach for diagnosis

History

1- **Ask about a family history** or known cause of jaundice e.g.

- Cirrhosis
- Hepatitis
- Gilbert Syndrome
- Dubin-Johnson syndrome
- Ulcerative colitis
- Sclerosing colangitis
- ?HIV?

2- **Type of surgery:**

- Upper abdominal surgery (hepatobiliary procedure) has higher risk for iatrogenic injury to bile ducts

3- **Type of anaesthesia:**

- Was a volatile gas used?
- Did the patient have a period of hypotension?

4- **Drug history:** Was the patient on

- Vasopressors?
- Phenytoin?
- Anti-TB drugs?

5- **Feeding**:

- Hepatic steatosis is more common when dextrose is the only caloric source. The Co-administration of lipids reduces the risk

6- **TPN**:
  - Cholestasis is uncommon in adult patients – more common in premature neonates
  - It usually develops after at least 3 weeks of administration

7- **The history of the onset** of the jaundice is helpful (time interval between operation and development of jaundice):
  - Onset within 48 hr to days after surgery in a previously healthy patient favour:
    - Hemolysis due to drugs (e.g. sulfa in G6PD ↓)
    - Breakdown of fragile transfused RBCs or transfusion reaction
    - Resorbtion of large hematoma
    - Acute rejection of a transplanted liver
    - Cardiopulmonary bypass or the insertion of a prosthetic valve
    - Gilbert syndrome
    - Dubin-Johnson syndrome
  - Onset 7 - 10 days after operation:
    - Medication-induced hepatitis attributable to an anesthetic agent
  - Onset within weeks:
    - Usually indicate intra-hepatic cause for the jaundice i.e. hepatitis or cholestasis but extrahepatic causes should always be excluded

8- **Pregnancy and Heart failure**: also predispose to postoperative jaundice

9- **Pruritis:** is caused by accumulating bile salts and not by bilirubin

Clinical examination

1- **Scleral icterus**

2- **Dark urine** = due to conjugated bilirubin filtered by the renal glomeruli (unconjugated bilirubin is tightly bound by albumin and not filtered or secreted)

3- **Acholic stools** (appear silvery):

- Mostly due to extrahepatic obstruction of the bile ducts

4- **Fever**:
  - Septicaemia
  - Cholangitis
  - Cholecystitis
  - Viral hepatitis
  - Malaria

5- **Right upper quadrant tenderness:**
  - Is a non-specific sign but a positive Murphy sign suggest cholecystitis

6- **Splenomegaly:**
  - May be seen with portal hypertension due to liver cirrhosis

7- Look and percuss for ascites

8- **Other signs of liver cirrhosis**
  - Gynecomastia
  - Testicular atrophy
  - Palmar erythema
  - Spider angiomata
  - Dupuytren's contractures

9- **Severely wasted and lymphadenopathy :**
  - Malignant biliary obstruction: often painless

10- **Encephalopathy** : may indicate acute liver failure

Biochemistry

1- **Urine dipstix:**
  - Conjugated bilirubin or hemoglobinuria

2- **Serum bilirubin**
  - Unconjugated hyperbilirubinemia = prehepatic causes
  - Conjugated hyperbilirubinemia = hepatocellular and posthepatic causes

3- **↑ reticulocyte count and ↓ haptoglobin levels**
  - Indicate hemolysis

4- **AST and LDH elevated:** with hemolysis

5- **ALT and ALP:** not significantly elevated with hemolysis

6- **↑ TLC and CRP:**
   - Indicate an underlying infection

7- **Peripheral blood smear**
   - May reveal abnormal red cell morphology

8- **Coombs-test** can help diagnose: immune hemolytic anemia

9- **In general, LFT's:** do not correlate with disease severity and do not help with the diagnosis in this group of patients
   - However, the ALT and AST are elevated much more than the ALP and GGT levels with hepatitis and the opposite usually occurs with posthepatic biliary obstruction
   - Marked elevations of serum aminotransferase levels (often to > 5000 U/L), + LDH indicates ischemic hepatitis due to trauma, shock or hyperthermia

10- To stratify a patient with liver disease according to the **Child-Pugh Classification**
   - PT must be done in addition to the serum albumin and serum bilirubin

11- **Drug levels:** ie. phenytoin, paracetamol

12- **If hepatits** is suspected do serology for hepatitis viruses A,B,C

13- **Do UKE:** remember hepatorenal syndrome

Hepatobiliary imaging

1- **Plain abdominal X-ray:**
   - Show gallbladder stones in only 15% of cases

2- **Ultrasound** -abdominal or endoscopic
   - Is the first-line imaging to be done
   - Sensitivity over 90% for detecting dilated extrahepatic bile ducts
   - Will also demonstrate gallbladder wall thickness and is the imaging technique of choice for the detection of stones within the gallbladder, but often misses stones in the common bile duct

3- **CT scan**

- Also highly sensitive for the detection of dilated bile ducts, but less sensitive for the detection of stones within the gallbladder
- Gives better definition of mass lesions/tumors
- May illustrate a bile leak or biloma after upper abdominal surgery

4- **ERCP**

- Gold standard for diagnosing biliary obstruction
- Diagnostic and therapeutic (Invasive)
- Sphincterotomy with removal of stones or stenting of the biliary stricture

5- **MRCP**

- Non-invasive alternative to ERCP for the diagnosis of biliary obstruction (not therapeutic)
- Indicated where ERCP is hazardous, difficult or impossible

6- **PCT** (percutaneous transhepatic cholangiography)

- May be useful for diagnosis and drainage of patients with biliary obstruction proximal to the hepatic duct
- Avoid in patients with suspected cholangitis, always give antibiotics

7- **Intra-operative cholangiography:**

- Indicated in all cases of cholecystectomy

8- **HIDA scan:**

- Can be done to confirm a diagnosis of cholecystitis

Pathophysiologic mechanisms

1- **Increased pigment load** (predominantly indirect hyperbilirubinemia)

- Resorption of hematoma or hemoperitoneum
- Transfusion:
  - 10% of erythrocytes in a unit of 14-day-old bank blood undergoing hemolysis within 24 hours of transfusion

- Hemolysis (rare):
    - Usually congenital erythrocyte defect, as G6PD deficiency or sickle cell disease
- Postcardiac surgery status:
    - Risk factors include preoperative elevations of serum bilirubin level and right atrial pressure, valve replacement (and number of valves replaced), and use of intra-aortic balloon counterpulsation;
    - In this setting, hyperbilirubinemia is a marker of increased mortality rate
- Inherited disorder of bilirubin metabolism (e.g., Gilbert's syndrome): may be coincidentally diagnosed after a surgical procedure

2- **Impaired hepatocellular function**

- Benign postoperative intrahepatic cholestasis:
    - Hepatocyte dysfunction from various stresses, such as hypoxemia, anesthesia, hemorrhage, sepsis, extensive transfusions
    - Often occurs in prolonged, difficult surgery with postoperative multiorgan failure
    - Peak serum bilirubin of up to 40 mg/dL on postoperative day 2 – 10 (may persist up to 3 weels) with variable elevation of alkaline phosphatase and mild elevation of aminotransferases
    - May mimic extrahepatic obstruction
    - Prognosis depends on the overall condition of the patient, not liver status; liver function returns to normal if patient recovers
- Hyperbilirubinemia of sepsis:
    - Triggered by bacterial infections, especially gram-negative sepsis and pneumococcal pneumonia
- Viral hepatitis:

- Hepatitis C: the most common cause of post-transfusion hepatitis (90% - 95% of cases); now rare; acute hepatitis occurs 6 - 7 weeks after transfusion
- Hepatitis B: also uncommon with contemporary serologic screening of donated blood; incubation period 12 - 14 weeks
- Rarely EBV, CMV, or hepatitis D (with B)

- Drug-related hepatitis:
  - Halothane:

    © Rare, with frequency of 1 in 35,000 exposures; onset of fever within 2- 10 days of exposure

    © Pathophysiologic mechanism involves immune sensitization to trifluoroacetylated liver proteins formed by oxidative metabolism of halothane by cytochrome P-450 2E1 in persons with a possible genetic predisposition
  - Enflurane: less common cause of hepatitis than halothane
  - Other drugs (e.g., erythromycin, sulfonamides, phenytoin, isoniazid, amoxicillinclavulanate; some drugs may cause intrahepatic cholestasis (e.g., chlorpromazine, anabolic steroids).
- Ischemic hepatitis (shock liver):
  - Due to trauma, shock or hyperthermia
  - Typically marked elevations of serum aminotransferase levels (often to > 5000 U/L), + LDH
  - Abrupt fall of ALT,AST and LDH with stabilization of the patient
  - Delayed ↑ in bilirubin up to 20 mg/dL often seen
- Total parenteral nutrition:
  - Possible associated with hepatomegaly
  - Minor elevations of serum aminotransferase
  - Fatty infiltration (may from high glucose load or possibly carnitine or choline deficiency)

- Intrahepatic cholestasis and nonspecific periportal inflammation (may from intravenous amino acids or fat emulsions and possibly toxic bile salts such as lithocholic acid)
- Fatty liver may be reversible with a decrease in the percentage of glucose or lecithin or choline supplementation

3- **Extrahepatic obstruction** (uncommon)

- Unrecognized bile duct injury with biloma formation, usually during cholecystectomy
- Cholangitis, subphrenic or subhepatic abscesses 2ry to biliary obstruction
- Choledocholithiasis, biliary or pancreatic tumor
- If biliary obstruction is suspected, evaluation with U/S or CT and cholangiography (MR cholangiopancreatography or ERCP) may be required

PBC & PSC

Primary biliary cirrhosis

Definition

PBC is a chronic cholestatic liver disease that usually affects middleaged women

Etiology

1- Combination of environmental and genetic factors
2- The human leukocyte antigen (HLA) and interleukin-12 signaling axis are particularly relevant biologically in the origin of this autoimmune small duct cholangitis

Incidence

1- PBC is a **female**-predominant (90% to 95%) disease seen in all ethnicities

2- An estimated 1 in 1000 **white women** who are **> 40 years** old have PBC

3- The age of onset: typically ranges from **30 - 70 years**, Diagnosis before menarche has not been reported

Pathogenesis

1- Chronic nonsuppurative **granulomatous cholangitis** is a better description of the disease than PBC, and at least 2 related processes appear to lead to hepatic damage

2- **The first process** is the chronic, often granulomatous, destruction of small bile ducts, presumably mediated by activated lymphocytes

- A component of autoimmune hepatitis cannot be excluded, and clinically a few patients (5% - 10%) have some evidence of this
- Bile duct cells in patients with PBC express increased amounts of class I HLA-A, HLA-B, and HLA-C and class II HLA-DR antigens, in contrast to normal bile duct cells

3- **The second process** includes chemical damage to hepatocytes in areas of liver where bile drainage is impeded by the destruction of the small bile ducts

- Retention of bile acids, bilirubin, copper, and other substances that are normally secreted or excreted into bile occurs
- The increased conc. of some of these substances, such as bile acids, may further damage liver cells
- Bile duct destruction eventually leads to portal inflammation and scarring and ultimately to cirrhosis and liver failure

Clinical features

Symptoms

- ■ 2/3 of patients are asymptomatic at the time of diagnosis
- ■ Most asymptomatic patients develop symptoms within 2-4 years
- ■ Symptoms and signs of PBC partly reflect cholestasis

1- Fatigue

- Most common symptom, but not specific to PBC

- Should consider nonhepatic disease such as depression, anemia, sleep apnea, hypothyroidism, and hypoadrenalism

2- Pruritus

- Pathogenesis: unknown but may be due to
    - Retention of the naturally occurring 1ry and 2ry bile acids
    - Another substance normally secreted into bile
    - Increased opioidergic tone related to chronic cholestasis
- Characteristically worse at bedtime
- May initially occur during the third trimester of pregnancy and persist after delivery
- Paradoxically often improved as disease progresses
- UDCA not a treatment for pruritus and may exacerbate itching

3- Osteoporosis

- In 25% of patients with PBC
- Frequent finding in healthy women of similar age
- Osteomalacia is now very uncommon
- Clinical symptoms: spontaneous or low-impact fractures, bone pain and vertebral decompression

4- Malabsorption

- Very uncommon clinical manifestation
- Manifestations include:
    - Nocturnal diarrhea
    - Foul-smelling bulky stools
    - And/or weight loss despite a good appetite and increased caloric intake
- Malabsorption of the fat-soluble vitamins A, D, E and K and calcium may be present
    - Night blindness is a particularly important symptom of vitamin A deficiency

5- Sicca complex

- Dry eyes, dry mouth, and vaginal dryness: frequent complaint
  - Some patients have true 1ry Sj◌gren's syndrome, although most do not

6- **Right-sided abdominal pain**

- Nonspecific pain occurs in 1/3 of patients

Physical examination

■ Findings depend on the stage of the disease

■ Examination usually normal in asymptomatic patients

1- **Hepatomegaly and splenomegaly**

- Seen with progressive disease
- Few patients may have splenomegaly early as a result of portal HTN 2ry to nodular regenerative hyperplasia

2- **Skin abnormalities**

- Hyperpigmentation → may resemble tanning and is caused by melanin, not bilirubin, in early-stage PBC
- Excoriations → may be diffuse from scratching caused by intractable pruritus
- Jaundice → usually manifests later
- Xanthelasmas and xanthomata → correlate with hypercholesterolemia
  - Xanthelasmas are more common than xanthomata
  - < 5% of patients will eventually develop xanthomata
  - Xanthomata are found on the palms of the hands and soles of the feet, over extensor surfaces of the elbows and knees, in tendons of the ankles and wrists, and on buttocks

3- **Eyes:**

- Kayser–Fleischer rings are rare and result from copper retention

4- **End-stage PBC:** (usually with cirrhosis and portal HTN)

- Spider telangiectases
- Temporal and proximal limb muscle wasting
- Ascites and edema

Diagnosis

Laboratory tests

1- **Liver biochemical tests**

- A cholestatic pattern (ALP/AST ratio usually < 3 and AST or ALT < five times the ULN) is observed
- Alone are never diagnostic of PBC
- ALP and GGTP elevations
  - The earliest abnormalities
  - The degree of elevation may relate to the severity of duct injury and the likelihood of treatment response
- ALT/AST persistent elevations on treatment: may relate to poorer long-term outcomes
- Serum bilirubin:
  - Usually normal early but elevated if the disease progresses
- It remains the strongest predictor of outcome

2- **AMA (antimitochondrial antibody)**

- Positive in 95% of patients
- PDH-E2 is the major autoantibody found in PBC

3- **Other associated findings**

- Serum albumin and PT: are normal in the early stages and abnormal in the late stage.
- Serum IgM: ↑
- Cholesterol: ↑ in 50% of patients
- HDL: ↑
- Hepatic and urinary copper: ↑
- Hypothyroidism: ↑TSH

Liver biopsy

1- Not routinely done

2- Confirm the diagnosis and determine disease severity at presentation

3- **Indications:**

  - In patients without AMA (and where specific ANA testing is not available)
  - In those with potential alternative explanations for liver biochemical test findings

Imaging

■ Useful to rule out bile duct obstruction and to screen for gallstones if significant pain is present

1- U/S:

  - Usually adequate to rule out bile duct obstruction

2- CT: if U/S is technically not feasible

3- Cholangiography:

  - Not needed except in AMA-negative patients in whom primary sclerosing cholangitis is a possible diagnosis; MRCP preferred in this setting

4- X-ray absorptiometry:

  - To assesses bone mineral density if PBC is diagnosed

Principles of diagnosis

1- The diagnosis is based on history, physical findings, laboratory tests and sometimes a liver biopsy

2- The combination of **cholestatic liver chemistries + positive AMA** test result gives a high positive predictive value for the histologic diagnosis of PBC

  - The diagnosis of PBC is now generally based on laboratory findings
  - 0.5% of the healthy population is AMA positive
  - 30% of healthy individuals may have fatty liver, which biochemically can be reflected by a rise in ALP

Differential diagnosis

1- Gallstones

2- Mechanical extrahepatic bile duct obstruction

  - Such as tumors, cysts, and postsurgical strictures

3- Primary sclerosing cholangitis (if AMA negative)

4- Nonalcoholic or alcoholic fatty liver

5- Cholestatic viral hepatitis

6- Granulomatous hepatitis

7- Autoimmune hepatitis

8- Vanishing bile duct syndrome

9- Benign, recurrent intrahepatic cholestasis

10- Drug-induced cholestasis

Treatment

Symptoms of chronic cholestasis

1- Pruritus

- Antihistamines
  - Symptomatically helpful early in the course of PBC when itching is not severe and the sedative side effects are favorable
- Cholestyramine
  - This nonabsorbed resin relieves pruritus in most patients
  - Therapy should be directed at symptomatic relief, with a usual dose of 4 g twice daily, generally taken mixed with water or juice before and after breakfast
  - Depending on the severity of cholestasis, it may take up to 14 days from the initiation of cholestyramine before the itching remits
  - Other medications need to be taken 1 hour before or 2 - 4 hours after cholestyramine, to avoid inadvertent binding to cholestyramine
- Colestipol hydrochloride (ammonium resin)
  - This is as effective as cholestyramine and may be used in patients who find cholestyramine unpalatable; some find colestipol equally unpalatable
- Other antipruritogenic agents that may control itching in some patients (listed in order of suggested use):
  - Rifampin (150 - 300 mg twice daily)

- Sertraline (50 - 100 mg once daily)
- Naloxone (opioid antagonist): based on data suggesting itching may be mediated by opioidergic neurotransmission
- Nalmefene (opioid antagonist)
- Naltrexone (opioid antagonist)
- Phototherapy with ultraviolet B light
- Large-volume plasmapheresis (almost always helpful but inconvenient and expensive)
- Molecular adsorbents recirculation system (MARS; effective where available)
- Liver transplantation

Drug	Mechanism of action	Dose	Side effects
Cholestyramine	Bile acid resin	4–16 g orally/day	Unpalatability, constipation, can interfere with absorption of medications
Colestipol	Bile acid resin	5 g orally 3 times/day	Constipation, can interfere with absorption of medications
Rifampin	Competes with bile acids for hepatic uptake	300–600 mg orally/day	Idiosyncratic hepatotoxicity
Sertraline	SSRI	50–100 mg/day	Dry mouth
Naloxone	Opioid antagonist	0.2 μg/kg IV/min for 24 hr	Self-limited opioid withdrawal–like syndrome
Nalmefene	Opioid antagonist	60–120 mg orally/day	Self-limited opioid withdrawal–like syndrome
Naltrexone	Opioid antagonist	50 mg orally/day	Self-limited opioid withdrawal–like syndrome

2- Malabsorption of fat-soluble vitamins

- Vitamins A, D, E, and K levels should be measured in jaundiced patients with PBC; patients with low levels should be treated
- Treatment: vitamins should be administered orally as far apart from cholestyramine as possible, because cholestyramine may bind and inhibit their absorption
  - Oral vitamin K: 5 mg/day

- Vitamin A: 10,000 - 25,000 IU/day
- 25-OH vitamin D: 20 µg 3 times weekly; check serum levels of 25-OH vitamin D after several weeks
- Supplemental calcium
- Vitamin E: 400 - 1000 IU/day

3- **Steatorrhea**

- Low-fat diet supplemented with medium-chain triglycerides (MCT) to maintain a reasonable caloric intake
- 60 mL of MCT oil per day
- Pancreatic replacement therapy: if concomitant pancreatic insufficiency with sicca syndrome
- Patients may develop iron deficiency anemia:
  - Which reflects unrecognized gastrointestinal blood loss, usually from changes of portal HTN in the stomach (gastropathy or gastric antral vascular ectasia)
  - Colonoscopy to exclude a lower gastrointestinal cause is appropriate before arriving at this conclusion

4- **Osteoporosis**

- Hormone replacement therapy: have beneficial effects in postmenopausal women with PBC
- Bisphosphonate etidronate: prevent corticosteroid-induced osteoporosis
- Liver transplantation:
  - Resulted in increased bone mineral density, but improvement is rarely noted until 1 year after transplantation
  - Bone mineral density decreases for up to 6 months after transplantation because of immunosuppression with glucocorticoids and physical inactivity

Underlying disease

1- **UDCA**

Drug	Mechanism	Dose	Benefits	Side	Comments

				effects	
Ursodeoxycholic Acid	Choleretic	13–15 mg/kg/ day orally	Improves liver biochemistry, Slows histologic progression, and probably improves long-term survival	Diarrhea, Mild weight gain (3kg), thinning of hair and bloating	Most widely used agent

- UDCA is the most widely used drug for PBC but is not curative and does not treat the underlying disease per se
- UDCA is safe and well tolerated
- If a patient responds biochemically to treatment, no recognized treatment “fatigue” occurs
- Stopping UDCA leads to a return in liver biochemical changes
- Mechanism of action:
    - Inhibiting absorption of toxic, endogenous bile salts
    - Stabilizing hepatocyte membranes against toxic bile salts
    - Replacing endogenous bile acids, some of which may be hepatotoxic
    - Reducing expression of major histocompatibility complex (MHC)
- Efficacy:
    - In 4 controlled trials, UDCA, at 13 - 15 mg/kg body weight/day orally, improved serum bilirubin, ALP, aminotransferase, and IgM levels
    - Decrease histological severity of interface hepatitis, inflammation, cholestasis & bile duct proliferation
    - Decreases significantly the risk of development of gastroesophageal varices, ascites & progression to cirrhosis
    - UDCA prolong the time before clinical deterioration & referral for liver transplantation
    - The greatest overall benefit is likely in patients with early disease, although a survival benefit is demonstrable only in those with advanced disease

- In a fourth, multicenter, study conducted in the United States, efficacy was limited to a subgroup of patients with stage I and II disease whose initial serum bilirubin level was < 2 mg/Dl
- One meta-analysis of clinical trials did not show that mortality or liver transplantation, or pruritus, fatigue, quality of life, liver histology, or portal pressures, were significantly improved by UDCA, given at a dose of 8 - 15 mg/kg per day for 3 months to 5 years
- Some studies, however, clearly showed that patients with a biochemical response to UDCA have normal life expectancy; the definition of response to therapy varies but generally includes the change in ALP value
- Further support for UDCA comes from the falling rates of transplantation for PBC parallel to the widespread use of UDCA

2- Colchicine:

- Early data were encouraging, but all available studies failed to find any strong evidence to support the use of this agent

3- Methotrexate:

- Early data were encouraging, but all available studies failed to find any strong evidence to support the use of this drug

4- New therapies

- Used for patients without a biochemical response to therapy with UDCA
- Suggestions have included budesonide, fenofibrates, and rituximab; however, data are not available to support routine use of these drugs
- Farnesoid X–receptor agonists appeared promising in phase II studies

Cirrhosis surveillance

1- **Varices** are usually associated with cirrhosis, but presinusoidal portal HTN is recognized

- Screen by endoscopy and uses disease severity (e.g., Mayo score), platelet count, and spleen size

  - Patients with fatigue may find beta blockade troublesome, thus necessitating prophylactic banding of varices

2- **HCC** is reported in cirrhotic patients with PBC; screening guidelines recommend surveillance at 6 – 12 month intervals by U/S if patients are cirrhotic

Liver transplantation

1- Patients with **end-stage PBC** are excellent candidates for liver transplantation; the MELD score is generally an appropriate way to identify patients likely to benefit

2- **End-stage PBC is generally defined as** cirrhosis complicated by the following:

  - Gastroesophageal variceal hemorrhage
  - Intractable ascites
  - Hepatic encephalopathy
  - Serum albumin < 3.5 g/dL
  - Serum bilirubin > 4 mg/dL

3- **One-year survival** approximately 90%.

4- PBC may **recur** in the allograft

5- **Cyclosporine** may protect against recurrent disease as compared with tacrolimus

Prognosis

1- Median survival of **symptomatic patients** ranges from 7½ - 10 years in different studies and is 7 years for histologic stages III and IV

2- If patients achieve a **biochemical response** to treatment with UDCA (e.g., 1 year after treatment, bilirubin is < ULN and AST < twice the ULN and ALP < 3 times the ULN, then 10-year survival is excellent, at 90%.

Primary sclerosing cholangitis

Definition

1- It’s a chronic **cholestatic** liver disease of middle-aged men

2- The disease is frequently found in association with **inflammatory bowel disease** usually ulcerative cholitis

Epidemiology

1- It's a **male-predominant** disease (about $^2/_3$ of patients).

2- Median age at diagnosis is **30-40 years**, it also can occur in children and older adults

3- Among patients with PSC, **60-80% has inflammatory bowel disease**, most commonly ulcerative colitis or Crohn's colitis

Genetics

1- Both genetic and environmental factors are involved, but evidence refers to a **defective inflammatory response** to intestinal microbial agents

2- The 100-fold increased risk of PSC in **first-degree relatives** suggests an important genetic component

Pathogenesis

1- Although PSC has been classified as an autoimmune disease, there are several **characteristics** which are not supportive of this theory such as:

  - Absence of female predominance
  - Absence of diseases-specific autoantibodies
  - Poor response to corticosteroids or immunosuppressive drugs

2- PSC may be more likely an **inflammatory disease** similar to inflammatory bowel disease, in which innate immune responses to bacterial pathogens are aberrant

3- **The main pathological features** include periductal fibrosis, inflammation, and bile duct proliferation alternating with ductal obliteration and ductopenia

Clinical features

1- **Symptoms:**

  - Fatigue: most common symptom

- Pruritus: the earliest specific complaint; it is characteristically worse at bedtime
- Right-sided abdominal pain

- Weight loss

2- **Physical examination:**

- Hepatomegaly
- Splenomegaly
- Skin abnormalities
  - Xanthomata (found on palm of hand, sole of foot, extensor surface of elbow & knee, tendons of ankle & wrist and on buttocks).
  - Excoriations due to Pruritus
  - Jaundice
- End-stage PBC: spider telangiectases, limb muscle wasting, ascites, and edema imply cirrhosis

3- **Associated diseases:**

- Inflammatory bowel disease:
  - No differences found in the course or severity of PSC in patients with or without IBD
  - The diagnosis of IBD usually precedes the diagnosis of PSC; however, PSC may occur prior
  - There is an increased risk of colorectal cancer in patients with PSC and ulcerative colitis compared with patients with ulcerative colitis alone
  - Treatment with UDCA may decrease the risk of colorectal cancer in patients with PSC and ulcerative colitis
- Type I diabetes
- Rheumatoid arthritis/arthropathy
- Autoimmune thyroiditis
- Psoriasis
- Celiac disease (Rare)

Differential diagnosis

1- Biliary stones

2- Caroli's disease

3- Cholangiocarcinoma

4- Ischemic stricture

5- HIV cholangiopathy

6- Exposure to biliary toxins e.g. formalin

7- Autoimmune pancreatitis with biliary involvement

8- Clonorchis infection

Diagnosis

1- **Liver biochemical tests:** cholestatic pattern

- ALP/GGT elevations
- Serum bilirubin is elevated
- ALP/AST ratio is elevated
- ALT & AST are elevated

2- **Imaging:**

- Radiologic features:
  - Diffuse multifocal annular strictures with intervening segments of normal or ectatic ducts
  - Short band-like strictures
  - Diverticulum-like saculations
- Techniques:
  - Endoscopic retrograde cholangiography (ERC) is the gold standard
  - Magnetic resonance cholangiography (MRC) is good alternate for ERC
  - Percutaneous transhepatic cholangiography (PTC).

3- **Serology:** autoantibodies found in patients with PSC:

- Perinuclear antineutrophil cytoplasmic antibodies (50-80%).
- Rheumatoid factor (4%).
- Smooth muscle antibodies (15%).
- Antinuclear antibodies (35%).

- Antithyroid (antiperoxidase, antithyroglobulin) antibodies (16%).

4- **Liver biopsy:**

- It's not indicated in cases with typical cholangiographic findings
- It's indicated for diagnosis of small duct PSC (i.e. normal cholangiographic findings).

- Small duct PSC refers to patients with histologic changes consistent with the classic form of PSC but without abnormal bile ducts on cholangiogram.
- IgG_4-related PSC is a disease related to autoimmune pancreatitis & may be separate entity from PSC.

Management

1- **Management of symptoms of chronic cholestasis:**

- See PBC

2- **Medical treatment of the underlying disease:** is disappointing

- UDCA: Biochemical improvement was common but at the highest dose of UDCA, but treatment was associated with an increase in death and liver transplantation
- Corticosteroids & immunosuppressives: have been studied but without significant effects **except**
  - Pediatric and adult PSC/AIH overlap
  - IgG_4-related cholangitis

3- **Endoscopic & radiologic therapy:**

- Has been demonstrated to improve jaundice and to relieve bacterial cholangitis
- However, long-term benefits of such therapies in halting disease progression haven't been demonstrated

4- **Biliary reconstructive surgical procedures:**

- Has been shown to relieve symptoms & have advantage of excluding CCA

- Moreover it has been associated with increased morbidity in patients who undergo liver transplantation

5- **Liver transplantation:**

- It's currently the treatment of choice for end-stage PSC
- It's associated with survival rates of 90% at 1-year & 85% at 5-years
- Recurrence of PSC occurs in up to 20-25% of patients at 5-10 years

Complications and their treatment

1- **Dominant strictures:**

- Defined as a stenosis with a diameter up to 1.5 mm in common bile duct or up to 1 mm in hepatic duct
- It most commonly occurs at perihilar region, should raise the suspension of CCA
- It occurs in 30-40% of patients with PSC
- Treated endoscopically or radiologically with balloon dilatation and stenting, in all cases, biliary histology and brush cytology should be obtained to exclude CCA

2- **Bacterial cholangitis:**

- It frequently occurs in patients with a previous biliary surgical procedure and obstructing dominant stricture
- Prophylaxis or on-demand therapy with ciprofloxacin is often effective

3- **Cholangiocarcinoma:**

- It carries a poor prognosis and doesn't respond well to chemotherapy or radiation
- CA19-9 level is often elevated in CCA, but is also elevated in bacterial cholangitis
- At cut-off value of 130 U/mL, the sensitivity and specificity are 79% and 98% respectively

4- **Gall bladder disease:**

- Among patients with PSC 25% develop gall stones, usually black pigment stones

- Patients with PSC are at high risk of gall bladder carcinoma and they should be screened annually with U/S
- Cholecystectomy should be considered in patients with gall bladder polyp or mass

5- **Peristomal varices:**

- Are common in patients who have undergone a proctocolectomy for underlying IBD and who have ileal stoma
- Bleeding can be controlled by performing surgical portosystemic shunt or TIPS
- Complications of peristomal varices can be prevented by performing an ileo-anal anastomotic surgical procedure in patients with PSC and IBD who need proctocolecomy

6- **Complications of chronic cholestasis: see PBC**

- Osteoporosis
- Malabsorption
- Hyperlipidemia
- Pruritus

Prognosis

1- **Cholangio-carcinoma** was reported to occur in up to 30% of patients

2- There is an increased risk of **colorectal cancer** in patients with PSC and ulcerative colitis compared with patients with ulcerative colitis alone

3- **Treatment with UDCA** may decrease the risk of colorectal cancer in patients with PSC and ulcerative colitis

Granulomatous liver disease

Definition

1- **Granulomas are** are rounded, 1- to 2-mm collections of activated macrophages, T lymphocytes, and other immune cells that infiltrate liver tissue as nodular lesions in response to a foreign or indigestible antigen or as a hypersensitivity reaction

2- **The principal immune cells** in granulomas are:
   - Activated macrophages resembling epithelial cells (epithelioid macrophages)
   - CD4+ T cells (T-helper, or Th, lymphocytes)
   - Sometimes multinucleated giant cells that develop from macrophage fusion

Pathogenesis

1- **The cause of the granuloma** influences the constituent immune cells and secreted products:
   - Th type 1 (Th1) cells and cytokines predominate in mycobacterial granulomas
   - Whereas Th2 cells and cytokines predominate in schistosomal granulomas

2- **Granulomas evolve by:**
   - The elaboration of secretory products (cytokines and chemokines) by their constituent cells (interferon gamma and interleukin-2 from Th lymphocytes)
   - Expansion of macrophage and T-cell pools
   - Specialization of macrophages for antigen digestion

3- **Granulomas ultimately** either resolve or undergo fibrosis or calcification

Incidence and location

1- Granulomas are found in 2.4% - 14.6% of liver biopsies, although a figure of **10%** is often quoted

2- Granulomas are found in **any of the following sites** in the liver, alone or in combination with the following:

- Lobular (tuberculosis, sarcoidosis, drugs)
- Portal/periportal (sarcoidosis)
- Periductal (primary biliary cirrhosis)
- Perivenous (mineral oil lipogranulomas)
- Periarterial/intra-arterial (phenytoin)

Morphological types

Type	Histologic features	Cause(s)
Caseating	Peripheral macrophages ± giant cells; central necrosis	Tuberculosis
Noncaseating	Cluster of macrophages ± giant cells	Sarcoidosis Drugs
Lipogranuloma	Lipid vacuole(s) surrounded by macrophages and lymphocytes	Fatty liver Mineral oil
Fibrin-ring (doughnut granuloma)	Central lipid vacuole or empty space Macrophages and lymphocytes Ring of fibrin	Q fever Allopurinol Hodgkin's L

Causes of hepatic granulomas

The etiology is **multifactorial**, but the major causes and examples are the following:

Etiology	Specific cause(s)
Infections	- Viral: cytomegalovirus infection, infectious mononucleosis, hepatitis C virus infection - Bacterial: brucellosis, tuberculosis - Rickettsial: Q fever - Spirochetal: T. pallidum infection - Fungal: histoplasmosis - Parasitic: schistosomiasis
Primary biliary cirrhosis	Early stages most commonly
Foreign bodies	Suture, talc
Systemic disease	Sarcoidosis, Crohn’s disease
Drugs	Allopurinol, phenytoin, penicillin
Neoplasia	Hodgkin’s lymphoma

Clinical features

1- **Symptoms and signs:** often include
  - Abdominal pain
  - Weight loss
  - Fatigue
  - Chills
  - Hepatomegaly
  - Splenomegaly
  - Lymphadenopathy
  - Fever of unknown origin

2- **Liver biochemical tests**
  - The liver biochemical test pattern is that of infiltrative disease:
    - ↑ serum alkaline phosphatase level is typical: 3 - 10 times normal
    - ALT and AST: usually normal or only mildly raised
  - Liver biochemical test levels may be normal

3- **Other laboratory tests**
  - Serum ACE level: ↑ in sarcoidosis, PBC, silicosis, and asbestosis
  - Serum globulin levels: ↑ in sarcoidosis, berylliosis, and chronic granulomatous disease of childhood
  - Peripheral blood eosinophilia: may be present with drug- or parasite-related granulomas

4- **Diagnostic work up of hepatic granuloma**
  - The cause may remain unknown in up to 50% of cases
  - Complete history of drug use
  - Test for antimitochondrial antibodies
  - ACE serum level
  - Staining liver specimens with acid fast for mycobacteria

  - Staining liver specimens with silver stain for fungi

Specific Types of Granulomatous Liver Disease

Sarcoidosis

1- Sarcoid granulomas preferentially cluster in **portal or periportal regions** and are associated with hyaline fibrosis

2- **Granulomas are noncaseating**, may contain inclusions (asteroid and Schaumann's bodies), and can be located within lobular parenchyma as well as in or near portal tracts

3- **Other pathologic features** may be seen:
  - Chronic intrahepatic cholestasis resulting from bile duct destruction
  - Bile duct damage resembling that seen in PBC
  - Periductal fibrosis resembling that seen in primary sclerosing cholangitis
  - Suppurative cholangitis
  - Granulomatous phlebitis
  - Hepatitis, including portal and lobular lymphocyte and plasma cell infiltrates with liver cell necrosis
  - Cirrhosis, but rarely

Tuberculosis

1- **Caseation** is seen in 29% of biopsy specimens and in 78% of autopsy specimens in patients with Mycobacterium tuberculosis infection

2- An **acid-fast stain** is infrequently positive (< 10% of proven cases).

3- Tuberculous granulomas may be found throughout the liver **parenchyma**

4- Rupture into bile ducts may result in tuberculous **cholangitis**

Schistosomiasis

1- The dense portal fibrosis seen grossly in advanced schistosomiasis is known as **Symmers' clay pipestem fibrosis**

2- **Schistosome eggs** arrive in portal vein radicles where granulomas are formed, with a peripheral rim of eosinophils

3- **Fine black hemozoin pigment** (derived from hemoglobin breakdown by adult worms) may be seen microscopically in macrophages within granulomas, portal tracts, and sinusoids

4- Patients with schistosomiasis should be tested for **hepatitis B and C viruses** because of common endemicity and contributions of viral infection to comorbidity

AIDS

1- **Acid-fast and silver stains** should be performed when granulomas are found in liver specimens from patients with AIDS

2- Granulomas resulting from **Mycobacterium avium complex** infection in patients with AIDS characteristically show:
  - Pale staining epithelioid macrophages containing linear structures (mycobacteria) on routine hematoxylin and eosin stain
  - Abundant, packed organisms in each macrophage on acid-fast stain

3- **Cytomegalovirus** hepatic infection occasionally results in small, noncaseating granulomas

4- **Other infections** identified in hepatic granulomas in patients with AIDS include histoplasmosis, cryptococcosis, and toxoplasmosis.

5- **Drugs used in AIDS** therapy (e.g., sulfonamides, isoniazid) may cause hepatic granulomas

Primary biliary cirrhosis

1- Granulomas may be seen in the livers of approximately **25% of patients** with PBC

2- Granulomas are usually seen **in earlier stages** of PBC, **in portal tracts** near damaged bile ducts

3- Occasionally, small, ill-defined histiocytic granulomas may be found within the **lobular parenchyma** (reported in 22.8% of PBC liver biopsy specimens)

Lipogranulomas

1. These result from **fatty liver or dietary mineral oil** ingestion (in laxative or food products).
2. They **consist of** fat vacuoles, scattered lymphocytes and macrophages, and strands of connective tissue
3. **Mineral oil lipogranulomas** are seen in portal tracts or near central veins or both
4. This type of granuloma has **no major clinical consequences**

Fibrin- ring (Doughnut) granulomas

1. **These granulomas consist of** a central vacuole or empty space, a surrounding pink ring of fibrin, epithelioid macrophages, and lymphocytes
2. Fibrin strands in these granulomas **can be stained with** the phosphotungstic acid– hematoxylin (PTAH) or Lendrum methods
3. **Nonspecific** because of their association with diverse conditions:
    - Q fever
    - Hodgkin's lymphoma
    - Allopurinol ingestion
    - Cytomegalovirus infection
    - Epstein-Barr virus infection
    - Leishmaniasis
    - Toxoplasmosis
    - Hepatitis A
    - Systemic lupus erythematosus
    - Giant cell arteritis
    - Staphylococcal infection
    - Boutonneuse fever (Rickettsia conorii)

Drug- related granulomas

1. Approximately **1/3** of hepatic granulomas may be caused by drugs
2. Drug-related granulomas may be found throughout the **hepatic parenchyma**, contain eosinophils, and be accompanied by other evidence of **drug hepatitis** (cholestasis, fat, hepatocyte ballooning, and apoptosis).
3. The list of causative drugs is extensive
4. Drug-related granulomas usually **heal without sequelae**

Miscellaneous granulomatous conditions

1- In children, **histoplasmosis** is an important etiologic consideration, particularly in endemic geographic regions

2- **Idiopathic granulomatous hepatitis** is seen in patients with fever of unknown origin and no established cause for the granulomas found on liver biopsy specimens

3- Patients with **chronic hepatitis C** may have small, noncaseating granulomas in their liver biopsies; these may recur after liver transplantation

Therapy

1- **Treatment of the causative agent**, when known, including:
  - Antibiotics for microbial infection
  - Removal of the implicated drug in drug-related cases
  - Corticosteroids for sarcoidosis

2- **In idiopathic granulomatous hepatitis:**
  - Disease may resolve spontaneously, with corticosteroid treatment, or with methotrexate

NUTRITION IN LIVER DISEASES

Hepatic encephalopathy ± HTN

Nutritional management

1- Patients with cirrhosis are unable to effectively store glycogen and rely on gluconeogenesis, an energy expensive process which utilizes amino acids to maintain adequate glucose levels. This **increases their daily energy and protein** requirement

2- It may be difficult to maintain oral intake in patients presenting with gastrointestinal bleeding and in those with severe encephalopathy. It may be necessary under these circumstances, to restrict dietary intake. A short period of dietary deprivation of up to 24 – 36 h may not be harmful **(NGT or TPN)** but prolonged restriction should be avoided then reintroducing gradually

3- Guidelines recommended daily **non protein energy intakes** of 35 – 45 Kcal/kg in decompensated cirrhosis (as in HE) & 25 – 35 Kcal/kg in compensated cirrhosis

4- Proteins

  - Protein turnover in cirrhotic patients is normal or increased
  - Stable cirrhotic patients are capable of achieving +ve nitrogen balance during aggressive nutritional support regime
  - Compensated cirrhosis → 1 – 1.2 g/kg body weight /day of protein or aminoacids

- Decompensated cirrhosis → protein intake should ↑ to 1.5 – 1.8 g/kg body weight /day (protein restriction is contraindicated)
- Stage 1 or 11 HE : protein intake should ↓ to 0.5 – 1.5 g/kg body weight/d
- Stage 111 or 1v HE: transient ↓ to 0.5 g/kg body weight/day Then ↑ protein to the limit of tolerance as HE improves
- Protein intake < 40 g/day contributes to malnutrition and worseness HE and leads to –ve nitrogen balance

5- **Vegetable protein** is better tolerated than animal protein; the benefits relate to the effects of dietary fiber on colonic function which include:

- ↓ in transit time and intraluminal PH
- ↑ in fecal ammonia excretion

6- Meal planning:

- It is important that food intake is spread evenly through out the waking day to avoid protein loading; 4-5 snack type meals with late evening meal containing about 50 g of CHO are preferable to 3 main meals
- Breakfast: try to be lesser in calories 20% with lower CHO max. of IR
- ↑ oral liquid supplements
- The late evening meal could alleviate the shift towards lipid oxidation by ↓ the length of time a patient fasts overnight {improve the nitrogen balance and ↑ non protein respiratory quotient}

7- Plasma branched chain amino acids (BCAA):

- Are reduced in patients with cirrhosis while plasma aromatic amino acids are increased. These disturbances have been linked to the changes in cerebral neurotransmitter balance observed in HE and thus attempts have been made to treat the syndrome with BCAA
- Significant increase in cerebral perfusion was observed in several brain areas following both I.V. and oral BCAA, suggesting a direct effect on cerebral function

- Conrroversial occur in use of BCAA, some studies concluded that it is has no effect and other suggest that BCAA supplementation may have beneficial effects on nutrition and progression free survival
- Examples : Nutri Hep Enteral Nutrition and Hepatic-Aid 11

8- Lipids

- Exess fat deteriorate liver condition
- < 30 % of total calories
- In underlying cholestasis (steatorrhea) → give MCT (medium-chain triglycerides)

9- Na

- Low salt diet (2 – 4 g/day) is best tolerated and accepted with more decrease in hypertensive patient
- Control Na intake leads to ↓ fluid retention and better response to diuretics after improvement of HE

10- Fluid restriction:

- If hyponatremia : to 0.5 – 1 L/day necessary only if the plasma Na <125mmol/L
- If no hyponatremia: a total of 1 – 1.5 L /day (2/3 with meals and 1/3 for thirst & medications)

11- **Zinc supplementation:** at doses of 600 mg/day for 3 months has shown to improve mental functioning in patients with HE

12- Micronutrients supplementation:

- Supplement all patients with CLD with calcium (1g/day) and vitamin D (800 iu/day), as up to 43% of patients undergoing transplant evaluation have osteoporosis
- Vitamin B,C , carnitine, selenium, chromium
- Antioxidants as vitamin E
- Patients with underluing alcoholic liver disease who continue to consume alcohol are at increases risk of ↓ of thiamine, folate and mg

- Patients with advanced liver disease esp. those with underlying cholestatic liver disease develop a ↓ of fat soluble vitamins
- Mg ↓ may be associated with poor control of blood sugar and ↑ IR

13- Probiotics

- The therapeutic benefit of acidifying the gut with synbiotics in cirrhotic patients with minimal HE was demonstrated
- Symbiotic/probiotic supplementation ameliorates hepatic function as reflected by bilirubin, albumin levels and PT
- Modulation of gut flora associated with a significant ↓ in blood ammonia levels and a reversal of minimal HE in 50% of patients

Newborn with galactosemia

Diet regemin

1- There is **no cure** for classic galactosemia

2- A special **galactose-free diet** is recommended

3- **Avoid all milk and milk-containing products** as much as possible for life, including:

- Breastmilk
- Cow's milk based baby formula
- Cow's milk, goat's milk, or dry milk
- Margarine, butter, cheese, ice cream, milk chocolate, or yogurt
- Foods that list nonfat dry milk solids, casein, sodium caseinate, whey, whey solids, curds, lactose, or galactose on the list of ingredients

4- Instead, newborns and infants should **drink a soy-based baby formula**, such as Enfamil Prosobee Lipil, Similac Isomil Advance, or Nestle Good Start Soy Plus, etc

5- If your baby doesn't tolerate a soy formula, **an elemental formula**, such as Nutramigen or Alimentum may be used instead, although they do have small amounts of galactose

6- **Older children** can drink a milk substitute made of isolated soy protein (Vitamite), or a rice drink (Rice Dream).

7- Children with galactosemia will also have to **avoid other foods** that are high in galactose, including liver, some fruits and vegetables, and certain dried beans, especially garbanzo beans. A registered dietitian or pediatric metabolic specialist can help you figure out which foods to avoid if your child has galactosemia and to help you make sure your child is getting enough calcium and other important minerals and vitamins

8- **Gal-1-p levels** can be followed to see if a child's diet has too much galactose in it

9- The dietary restriction of children with variant galactosemia are more **controversial**:

- One protocol involves restricting milk and milk-containing products, including breastmilk, for the first year of life, and then allowing some galactose in the diet once the child is a year old
- Another option is to allow an unrestricted diet and watch for an elevation of gal-1-p levels

10- Children with classic galactosemia can also sometimes, even when they follow a strict diet, be **at risk for** short stature, learning disabilities, gait and balance problems, tremors, speech and language disorders, and premature ovarian failure

Child with acute viral hepatitis

No specific dietary recommendation

1- Maintenance of adequate caloric and fluid **intake**

2- Large **breakfast** possibly the best tolerated meal

3- Avoid **alcohol** for 3- 6 months

4- Avoid all nonessential **drugs** e.g. vitamins, amino acids and lipotropic agents

5- **Low fat , high carbohydrate** diet is popular because it has proved the most palatable to anorexic patient

6- But **no benefit** accrues from a rigid insistence upon a low fat diet

7- If dehydration occur because of repeated vomiting → **I.V. fluids** (glucose)

Diet regimen

1- Appetite stimulation

- Offer the patient his or her favourite fat-free or low-fat foods (see below for tips on selecting a low-fat diet), for example
- Fruit juices, energy drinks (Lucozade, Powerade, Energade or Game diluted with cold water)
- Fat-free milk shakes or smoothies (make from fresh or canned fruit, fat-free milk or yoghurt to which you can add flavouring, honey and fat-free milk powder to boost the protein and energy content)
- 'Slush-puppies' and sorbets made from pureed fruit and sugar which is then frozen, custard made with fat-free milk, jelly and jelly-Ideal Milk desserts
- Low-fat ice cream, clear soups (chill overnight and remove the fat that coagulates on top of the soup), dry crackers and rusks, bland porridges with fat-free milk and sugar to boost energy intake, hard or boiled sweets, and any other food that the patient is prepared to eat

2- Tips to improve food intake:

- Serve the above mentioned foods and beverages chilled as this helps to overcome nausea
- Let the patient eat a dry biscuit or rusk before eating other foods as this can assist with food aversion
- Add slightly more flavouring to milk shakes, smoothies and custard to overcome loss of taste sensation
- Serve patient with small quantities more often so that they don't get discouraged if they are only able to drink or eat small portions at a time

3- Use of liquid meal replacements

- Use high-energy, high-protein meal replacement products as, Ensure, or Nutren Optimum and Nutren Fibre

4- Avoid the folloing foods:

a. Full-cream milk, yoghurt, cream, cream cheese and fatty cheeses

b. Biscuits, cakes, pies, tarts, etc with a high-fat content
c. Chocolate
d. Not more than three eggs a week
e. Fatty salad dressings, mayonnaise, sour cream
f. Avocado
g. Fatty, fried meats, fatty fish, poultry skin, all processed meats and sausages, bacon, fatty gravies, fish canned in oil (buy tuna or pilchards canned in water or tomato sauce)
h. Nuts, peanut butter, nut spreads
i. Potato chips, vegetables smothered in butter or white/cheese sauces
j. Fatty snacks or very spicy snacks
k. All food preparation that increases the amount of fat contained in meals, such as frying in butter, margarine or oil. Rather boil, poach, grill, cook in a nonstick pan with Spray and Cook, and cook stews and soups the day before, chill and skim off all the coagulated fat before serving.

Diabetic patient with hepatic ascites

Nutritional management

1- Patients with cirrhosis are unable to effectively store glycogen and rely on gluconeogenesis, an energy expensive process which utilizes amino acids to maintain adequate glucose levels. This **increases their daily energy and protein** requirement

2- **Meal planning:**

- It is important that food intake is spread evenly through out the waking day to avoid protein loading; 4-5 snack type meals with late evening meal containing about 50 g of CHO are preferable to 3 main meals
- Breakfast: try to be lesser in calories 20% with lower CHO max. of IR
- ↑ oral liquid supplements
- The late evening meal could alleviate the shift towards lipid oxidation by ↓ the length of time a patient fasts overnight {improve the nitrogen balance and ↑ non protein respiratory quotient}

3- **Sodium restriction is the mainstay of treatment:**

- Sodium balance occurs when sodium intake = sodium loss
- Na intake = dietary intake + all medically related Na administration

- Na loss = insensible (≈ 5 mmol/day) + fecal (≈ 5 mmol/day) + urinary sodium excretion
- The goal is: Na intake of 2 gm/day (88mmol/day)
- A low salt diet alone eliminates ascites in only 10% of patients
- In severe cases: Na restriction to 22 mmol/day (0.5 gm/day) is necessary

4- **Water restriction:**

- If hyponatremia : to 0.5 – 1 L/day necessary only if the plasma Na < 125mmol/L
- If no hyponatremia: a total of 1 – 1.5 L /day (2/3 with meals and 1/3 for thirst & medications)

5- **CHO controlled diets:**

- Minimal amount → 400 g / day
- No restriction even in IR or frank diabetes
- 70 % total calories
- Of which 60 – 70 % are complex CHO
- Should be distributed all through the day in every meal

6- **Potassium supplementation**

7- **Gastroparesis:**

- Delayed or irregular contractions of the stomach
- Symptoms: include feelings of fullness, bloating, nausea, vomiting, diarrhea or constipation
- Can affect blood glucose control
- Treatment:
    - Small frequent meals
    - Low fiber and fat
    - Liquid meals if necessary
    - May need to take insulin after the meal
    - Frequent blood glucose monitoring

8- Guidelines recommended daily **non protein energy intakes** of 35 – 45 Kcal/kg in decompensated cirrhosis (as in ascites) & 25 – 35 Kcal/kg in compensated cirrhosis

9- Proteins

- Protein turnover in cirrhotic patients is normal or increased
- Stable cirrhotic patients are capable of achieving +ve nitrogen balance during aggressive nutritional support regime
- Compensated cirrhosis → 1 – 1.2 g/kg body weight /day of protein or aminoacids
- Decompensated cirrhosis → protein intake should ↑ to 1.5 – 1.8 g/kg body weight /day (protein restriction is contraindicated)

10- Vegetable protein is better tolerated than animal protein; the benefits relate to the effects of dietary fiber on colonic function which include:

- ↓ in transit time and intraluminal PH
- ↑ in fecal ammonia excretion

11- Lipids

- Exess fat deteriorate liver condition
- < 30 % of total calories
- In underlying cholestasis (steatorrhea) → give MCT (medium-chain triglycerides)

12- Micronutrients supplementation:

- Supplement all patients with CLD with calcium (1g/day) and vitamin D (800 iu/day), as up to 43% of patients undergoing transplant evaluation have osteoporosis
- Vitamin B,C , carnitine, selenium, chromium and zinc
- Antioxidants as vitamin E
- Patients with underluing alcoholic liver disease who continue to consume alcohol are at increases risk of ↓ of thiamine, folate and mg

- Patients with advanced liver disease esp. those with underlying cholestatic liver disease develop a ↓ of fat soluble vitamins
- Mg ↓ may be associated with poor control of blood sugar and ↑ IR

DIAGNOSTIC STUDIES

Liver biopsy

The definitive test for the following:

1- To **confirm the diagnosis** of specific liver diseases
  - Such as Wilson disease, small duct primary sclerosing cholangitis, and nonalcoholic fatty liver disease

2- To assess **prognosis** in most forms of parenchymal liver disease
  - Such as chronic viral hepatitis

3- To evaluate **allograft** dysfunction
  - In liver transplant recipients

Indications

1- Evaluation of abnormal **liver biochemical test** levels and **hepatomegaly**

2- Evaluation and staging of **chronic hepatitis**

3- Identification and staging of **alcoholic** liver disease

4- Recognition of systemic inflammatory or **granulomatous** disorders

5- Evaluation of **fever** of unknown origin

6- Evaluation of the pattern and extent of **drug**-induced liver injury

7- Identification and determination of the nature of **intrahepatic masses**

8- Diagnosis of multisystem **infiltrative** disorders

9- Evaluation and staging of **cholestatic** liver disease (primary biliary cirrhosis, primary sclerosing cholangitis)

10- **Screening** of relatives of patients with familial diseases

11- Obtaining tissue to culture **infectious** agents (e.g., mycobacteria)

12- Evaluation of effectiveness of **therapies** for liver diseases (e.g., Wilson disease, hemochromatosis, autoimmune hepatitis, chronic viral hepatitis)

13- Evaluation of liver biochemical test abnormalities following **transplantation**

Contraindications

- In patients with **renal insufficiency**, uremic platelet dysfunction should be corrected by infusion of arginine vasopressin (DDAVP) (0.3 µg/kg in 50 mL N saline intravenously) immediately before biopsy
- **Aspirin and NSAIDs**, which may also produce platelet dysfunction, are prohibited for 7 - 10 days before elective liver biopsy

Absolute	Relative
- History of unexplained bleeding - PT >3–4 sec over control - Platelets <60,000/mm3 - Prolonged bleeding time (>10 min) - Unavailability of blood transfusion support - Suspected hemangioma - Uncooperative patient	- Ascites - Infections in right pleural cavity - Infection below right diaphragm - Suspected echinococcal disease - Morbid obesity

Complications

1- **Post-biopsy pain:**

- ± Radiation to the right shoulder occurs in up to 1/3 of patients.
- Vasovagal reactions are also common.
- Serious complications are uncommon (< 3%) and usually manifest within several hours of the biopsy.
- The fatality rate is 0.03% to 0.32%.

2- **Intraperitoneal bleeding:**

- Is the most serious complication.
- Increasing age, the presence of hepatic malignancy, and the number of passes made are predictors of the likelihood of bleeding, as is the use of a cutting needle rather than a suction needle.
- Serious bleeding may be controlled by selective embolization at angiography or, if necessary, ligation of the right hepatic artery or hepatic resection.

3- **Pneumothorax:**

- May require a chest tube

4- **Hospital admission**

- May be required for patients who have clinical evidence of hemodynamically significant bleeding, persistent pain unrelieved by analgesia, or other evidence of a serious complication

5- **Biopsy of a malignant neoplasm**

- Carries a 1% - 3% risk of seeding of the biopsy tract with tumor

Technique

1- Liver biopsy can be performed safely on an **outpatient basis**:

- If none of the contraindications are present and the patient can be adequately observed for at least 3 hours following the procedure, with access to hospitalization if necessary (required in up to 5% of patients).

2- **A local anesthetic**:

- Is infiltrated subcutaneously and into the intercostal muscle and peritoneum.
- A short-acting sedative may be given to allay anxiety.
- Percussion at the bedside identifies the point of maximal hepatic dullness

3- The routine use of **ultrasonography** to mark the biopsy site or guide the biopsy needle has become frequent.

- In diffuse liver disease, ultrasound-guided liver biopsy may be associated with a higher yield and lower rate of complications than blind biopsy

4- **A transthoracic approach** is standard

- A subcostal approach should be attempted only with ultrasound guidance

5- The biopsy is performed **at end-expiration**; various needles (cutting [Tru-Cut, Vim- Silverman] or suction [Menghini, Klatskin, Jamshidi]) are used, including a biopsy "gun."

6- **The biopsy site** :

- Is tamponaded by having the patient lie on the right side

7- **Transjugular biopsy** may be performed

- When the standard approach is contraindicated (e.g., coagulopathy or ascites):
- This technique also allows determination of the hepatic venous wedge pressure gradiant to confirm portal hypertension, assess reponse to beta-blocker therapy, and determine prognosis

8- **Focal hepatic lesions**:

- Are best sampled for biopsy under radiologic guidance

9- **An adequate specimen** for histologic interpretation:

- Is at least 1.5 cm long and contains at least 6 portal triads

Hepatic imaging

1-Plain abdominal x-ray studies: of little value

- Occasionally, **calcifications** seen which usually result from:
  - Gallstones
  - Echinococcal cysts
  - Old lesions of tuberculosis or histoplasmosis
  - Tumors or vascular lesions may also be calcified.

2-Barium swallow:

- Less sensitive than endoscopy for detecting **esophageal varices**.

3-Wireless video capsule endoscopy:

- Used also to screen for **esophageal varices.**

4-U/S

- This is the initial radiologic study **of choice**
- **Contrast agents** have been introduced to enhance the accuracy of ultrasonography; these include:
  - A micro-bubble technique for detection of discrete lesions
  - Galactose-based contrast agents to assess vascularity

- **Limitations:**
  - U/S cannot penetrate gas or bone, a characteristic that may preclude adequate examination of the viscera.
  - Furthermore, increased resolution is generally at the expense of decreased tissue penetration
- **Values:**
  - Real time U/S demonstrates physiologic events such as arterial pulsation.
  - Better at detecting focal lesions than parenchymal disease
  - The initial test of choice to detect biliary dilatation.
  - May detects hepatic masses as small as 1 cm
  - May distinguishes cystic lesions from solid ones.
  - Facilitate percutaneous biopsy of solid hepatic masses, drainage of hepatic abscesses, or paracentesis of loculated ascites
  - U/S with the Doppler technique is used to assess the patency of hepatic and portal vasculature in liver transplant candidates and recipients

5-CT scan:

- **Principle:**
  - Oral contrast defines the bowel lumen and intravenous contrast enhances vascular structures increase anatomic definition
- **Values:**
  - CT with intravenous contrast:

    © Excellent way to identify and characterize hepatic masses

    © Cystic and solid masses can be distinguished, as can abscesses.

© identify cavernous hemangiomas

© Neoplastic vascular invasion may also be identified.

© HCC exhibits rapid arterial enhancement and venous “washout” from the blood supply from the arterial rather than the portal system

- CT portography with intravenous contrast:

  © enhances the sensitivity of lesion detection within the liver

- Lipiodol:

  © Is preferentially taken up and retained by HCC and can be used as a contrast agent to detect small (up to 5 mm) neoplastic lesions

- CT can also suggest the presence of:

  © Cirrhosis and portal hypertension

  © Changes consistent with fatty liver or hemochromatosis

- **Limitations:**
  - Cost, radiation exposure, and lack of portability

6- MRI

- **Values:**
  - Excellent method for evaluating blood flow and can detect hepatic iron overload
  - The imaging study of choice in confirming the presence of vascular lesions, notably hemangiomas
  - It is also useful in differentiating regenerating nodules from HCC

    © On a T2-weighted image, the signal intensity of a regenerating nodule is equivalent to that of normal hepatic parenchyma

    © Whereas that of a carcinoma is higher
  - Use of liver-specific contrast media further enhances the accuracy of assessing hepatic mass characteristics by MRI
- **Limitations:**
  - Unlike CT, MRI does not require ionizing radiation, but concern is increasing about the syndrome of nephrogenic systemic fibrosis in patients with impaired renal function after the use of gadolinium contrast

- **MRCP:**
  - Alternative to diagnostic endoscopic cholangiopancreatography
- **Magnetic resonance angiography:**
  - Has become a useful method to assess the hepatic vasculature before hepatic resection

7- Radioisotope scanning

- **Principle:**
  - Technetium-99m (99mTc)–labeled sulfur colloid is used for anatomic evaluation of the liver and is taken up by Kupffer cells. Any process such as a neoplasm, cyst, or abscess that replaces those cells results in a “cold” area. Lesions greater than 2 cm in diameter can usually be detected
- **Values:**
  - Particularly helpful in the assessment of suspected acute cholecystitis
  - The caudate lobe of the liver, because of its independent venous drainage, may be unaffected by obstruction of the hepatic vein in Budd–Chiari syndrome and thus may have preferential uptake of isotope
  - For parenchymal and focal liver disease, U/S and CT have largely superseded nuclear medicine studies

8- PET

- **Value:**
  - Detects increased glucose metabolism characteristic of hepatic neoplasm
  - Clinical applications include detection and staging of primary hepatic malignant diseases, evaluation of metastatic disease, and differentiation of benign from malignant hepatic tumors
- **Limitations:**

- The accuracy of PET in HCC is limited by poor uptake of the most commonly used radiopharmaceutical (18F-fluoro-2-deoxyglucose [FDG]) by well-differentiated tumors

9-Transient elastography

- **Principle:**
    - This technique incorporates an ultrasound transducer probe mounted on a vibrator to induce an elastic shear wave to measure hepatic stiffness, which reflects fibrosis, in a cylinder 1 cm wide and 4 cm long.
    - The results are expressed in kilopascals (kPa) and range from 2.5 to 75 kPa, with normal values approximately 5.5 kPa
- **Value:**
    - It is most accurate for detecting advanced fibrosis and cirrhosis
    - Magnetic elastography uses magnetic resonance to measure liver stiffness
- **limitations:**
    - It is technically difficult in obese patients or if ascites is present
    - Considerable overlap exists between stages when fibrosis is less extensive
- It may complement rather than replace liver biopsy

Approach to use of imaging studies in hepatic diseases

Clinical problem	Initial imaging	Supplemental imaging studies (if necessary)
Jaundice	US	CT, if dilated ducts, to detect obstructing lesion or, if suspicion of a mass in the pancreas or porta hepatis; MRCP to determine site and cause of dilated ducts
Hepatic parenchymal Disease	US CT MRI	Doppler US, color Doppler US, or MRI with flow sequences if a vascular abnormality is suspected and in some

		instances of portal hypertension
Screening for liver mass	US	CT, MRI
Characterizing known liver Mass	CT, MRI	
Suspected malignancy	US- or CT-directed biopsy	CT portogram, intraoperative US
Suspected benign lesion	US, CT, or MRI; nuclear medicine scan (e.g., 99mTc-labeled red blood cell scan) for suspected hemangioma	US- or CT-directed biopsy
Suspected abscess	US or CT US- or CT-directed aspiration	Nuclear medicine abscess scan (gallium or 111In-labeled white blood cell scan)
Suspected biliary duct Abnormalities	US to detect dilatation, biliary stones, or mass MRCP, ERCP, or THC to define ductal anatomy	CT or endoscopic US to detect stones or cause of extrinsic compression

THC, transhepatic cholangiography

The liver in pregnancy

Overview

Liver disorders with pregnancy

Unique to pregnancy	Coincidentally with pregnancy

Hyperemesis gravidarium Intrahepatic cholestasis of pregnancy Acute fatty liver of pregnancy Pre-eclampsia/eclampsia HELLP syndrome Hepatic rupture	Viral hepatitis Budd-Chiari syndrome Cholelithiasis and cholecystitis Wilson disease Autoimmune hepatitis

Changes in liver biochemical test levels in normal pregnancy

Test	Change	Trimester of max. change
Albumin	↓ 10-60%	2nd
Gamma globulins	None to slight ↓	Third
Fibrinogen	↑ 50%	2nd
Transferrin	↑	Third
Bilirubin	None	----
Alkaline phosphatase	↑ 2-4 fold	Third
AST	None	----
ALT	None	----
Cholesterol	↑ 2 fold	Third

Hyperemesis gravidarum

1- Definition:

- Intractable vomiting in pregnancy that leads to:
  - Dehydration
  - Electrolyte disturbances
  - Weight loss of 5% or more
  - Nutritional deficiencies

2- Epidemiology:

- Most common in first trimester
- Incidence: 0.3% to 2%
- Risk factors:
  - Age < 25 years
  - Preexisting diabetes mellitus
  - Hyperthyroidism

- Overweight
- Primiparity
- Multiple gestations
- Prior history of hyperemesis gravidarum
- Molar pregnancy

3- Etiology:

- Thought to be multifactorial involving immunologic, hormonal, and psychological factors

4- Clinical and laboratory features:

- Liver biochemical test abnormalities in 50% of patients
- Serum alanine aminotransferase (ALT) elevations generally 1- to 3-fold but may reach 20 times the upper limit of normal
- Occasional serum alkaline phosphatase and bilirubin elevations
- Concomitant hyperthyroidism in 50%

5- Diagnosis: clinical.

6- Treatment: Supportive

- Rehydration
- Vitamin supplementation
- Small and frequent low-fat meals
- Antiemetics e.g.,
  - Metoclopramide 10 to 30 mg orally 4 times daily or 10 mg intramuscularly or intravenously every 4 to 6 hours
  - Or ondansetron 4 - 8 mg orally every 8 hours or 8 mg intravenously every 4 to 8 hours
- Total parenteral nutrition possibly needed in severe cases

7- Outcome:

- Observed lower rate of spontaneous abortion
- Lower birth weights
- Increased incidence of congenital hip dysplasia in infants

Intrahepatic cholestasis of pregnancy

1- Definition:

- Reversible form of cholestasis characterized by:
  - Intense pruritus in pregnancy
  - Elevated serum ALT
  - Elevated fasting serum bile acid levels
  - Spontaneous relief of symptoms and signs within 4 - 6 weeks after delivery

2- Epidemiology

- More common in late second or third trimester, but can occur in any trimester
- Incidence:
  - 0.01% to 2%
  - With higher incidence in South Asian, South American, and Scandinavian populations
  - Highest incidence (up to 27%) in Chilean Araucanian Indians
- Risk factors:
  - Progesterone use in pregnancy
  - Past medical or family history of IHCP
  - Personal history of intrahepatic cholestasis resulting from oral contraceptive or estrogen ingestion

3- Etiology: Multifactorial, including genetic, hormonal, and environmental factors. Theories include the following:

- Gene variants of hepatocanalicular transport proteins:
  - (ATP-binding cassette [ABC] transporter B4 = phosphatidylcholine floppase, ABC transporter B11 = bile salt export pump, ABC transporter C2 = conjugated organic anion transporter, ATP8B1 = FIC1) and their regulators (e.g., the bile acid sensor farnesoid X receptor, FXR) found in some patients;

    - incidence of IHCP increased in mothers of children with progressive familial intrahepatic cholestasis (PFIC) type 3
- Inherited sensitivity to estrogens
- Association with low serum selenium levels; decreasing incidence in Chilean population linked to increases in serum selenium levels

4- Clinical and laboratory features

- Jaundice in 25% of patients and following the onset of pruritus
- Elevated serum levels of
    - Aminotransferase levels (up to four-fold)
    - Serum bile acid levels (30–100x)
    - Mono- or disulfated progesterone metabolites (particularly 3- and 5-alpha isomers)
    - Serum cholesterol and triglyceride levels (occasionally)
- Liver biopsy:
    - Not usually indicated
    - Specimens reveal cholestasis with minimal hepatocellular necrosis

5- Diagnosis: clinical.

6- Treatment

- Symptom management:
    - Sleeping in a cold room
    - Topical alcohol and camphor menthol lotion
    - Cholestyramine, and ursodeoxycholic acid (UDCA) 10 - 15 mg/kg body weight
- Close monitoring and early delivery of fetus

7- Outcome

- Mothers do well
- Increased risk of following particularly when fasting serum bile acid levels are > 40 µmol/L
    - Preterm delivery (19% to 60%)

- Meconium staining of amniotic fluid (24%)
- Fetal bradycardia (14%)
- Fetal distress (22% to 41%)
- Fetal loss (0.4% on average; 4.1% in severe cases)

Acute fatty liver of pregnancy

1- Definition:

- A rare life-threatening complication of pregnancy
- Manifested by microvesicular fatty infiltration of the liver and progressive liver failure

2- Epidemiology:

- Onset in third trimester (usually after 35th week, but as early as 26 weeks; can occur in the immediate postpartum period)
- Incidence: 1 in 10,000 to 15,000 deliveries
- Risk factors: primiparity, multiple gestations, and male fetuses

3- Etiology:

- **Defects in mitochondrial fatty acid beta-oxidation** in the mother caused by fetal deficiency in the long-chain 3-hydroxyacyl-coenzyme A dehydrogenase (LCHAD) enzyme.
- **LCHAD** is part of mitochondrial trifunctional protein (MTP) and catalyzes the third step in β-oxidation of long-chain fatty acids. Up to 70% of cases result from homozygous longchain LCHAD deficiency in the fetus, with a heterozygous mother
- Abnormal concentrations of fetal long-chain fatty acids enter the maternal circulation and have toxic effects in the mother
- **G1528C** (E474Q mutation) in the MTP causes LCHAD deficiency
- **A second fatty-acid oxidation defect**—hepatic carnitine palmitoyl transferase I deficiency— is also associated with maternal AFLP

- **Other proposed pathogenic factors include:** nutritional factors, alterations in lipoprotein synthesis, and enzyme deficiencies in the mitochondrial urea cycle

4- Clinical and laboratory features

- **Clinical:**
  - Symptoms include headache, fatigue, malaise, nausea, vomiting, and abdominal pain
  - Jaundice may follow a prodrome
  - Progressive liver failure may occur, with coagulopathy, encephalopathy, or renal failure
  - 50% of patients have signs of pre-eclampsia
- **Laboratory:**
  - Serum aminotransferase levels are elevated (usually less than 500 U/L)
  - Serum alkaline phosphatase and bilirubin levels are mildly to moderately elevated
  - Hyperuricemia occurs in 80%

5- Diagnosis

- Abdominal U/S and CT are inconsistent in detecting fatty infiltration
- If the disorder and a risk to delivering a premature infant are clinically suspected, then emergency **liver biopsy** should be done.
- The frozen liver biopsy specimen shows a microvesicular fatty infiltrate of liver detectable by Oil-Red-O stain

6- Treatment

- **Rapid delivery** of the infant is critical.
- Most women improve, but fulminant hepatic failure may occur, and treatment with liver transplantation has been reported
- **Screening** for a fatty acid oxidation defect is indicated in affected patients

7- Outcome

- Maternal mortality rate of 8% - 18%
- Fetal mortality rate of 18% - 23%

Pre-Eclampsia/Eclampsia

1- Definition:

- The **triad** of hypertension, proteinuria, and edema.
- Pre-eclampsia is a **multisystem** disease with renal, hematologic, hepatic, central nervous system, and fetal-placental involvement.
- Eclampsia is the presence of **convulsions or coma** in addition to the symptoms and signs of pre-eclampsia

2- Epidemiology

- More common in late second or third trimester, but may occur postpartum
- **Incidence**: pre-eclampsia in 5% - 7% of pregnancies, eclampsia in 0.1% - 0.2%
- **Risk factors:** insulin resistance, obesity, extremes of maternal age (age less than 20 or more than 45 years), primiparity, infection, family history of pre-eclampsia/eclampsia, multiple gestations, hydatidiform mole, fetal hydrops, polyhydramnios, and inadequate prenatal care

3- Etiology:

- Unknown.
- **Proposed mechanisms include:**
  - Vasospasm
  - Abnormal placental development
  - Abnormal endothelial reactivity
  - Activation of coagulation
  - Decreased nitric oxide synthesis.

- Levels of fms-like tyrosine kinase 1 (sFlt1; also known as soluble vascular endothelial growth factor) are high, and up-regulation of placental endoglin occurs.
- A mutation in the gene encoding STOX1 transcription factor has been proposed to cause susceptibility, but data are still not clear

4- Clinical and laboratory features

- **Hypertension**
  - Mild Mild pre-eclampsia: blood pressure 140/90 mm Hg or higher but lower than 160/110 mmHg
  - Severe pre-eclampsia: blood pressure 160/110 mm Hg or higher
- **Convulsions or coma** in eclampsia
- Headaches, visual changes, abdominal pain, heart failure, respiratory distress, and oliguria are possible **in severe disease**

5- Diagnosis

- Clinical features suggest the diagnosis
- **Serum aminotransferase levels** are elevated in 90% of patients with eclampsia, 50% with severe pre-eclampsia, and 24% with mild pre-eclampsia
- Serum aminotransferase levels are elevated 5 - 100 times, with modest increases in serum bilirubin levels (up to 5 mg/dL)
- Thrombocytopenia and microangiopathic hemolytic anemia may occur
- **Liver biopsy** specimens, if available, may demonstrate periportal deposition of fibrin and fibrinogen associated with hemorrhage, with or without necrosis. In some cases, microvesicular fatty infiltration is seen, suggesting overlap with AFLP

6- Treatment

- **Delivery of the infant** is the preferred treatment of eclampsia and near-term pre-eclampsia.

- **Management remote from term** is controversial but may include bed rest, antihypertensive therapy, and magnesium sulfate
- The incidence of pre-eclampsia is **not** reduced with nutritional supplementation, including calcium, or with low-dose aspirin

7- Outcome

- The most common cause of death is **cerebral involvement**
- The risk of **hepatic rupture and HELLP** syndrome is increased
- **Risks to the fetus** include:
  - Prematurity
  - Fetal growth retardation
  - Abruptio placentae
  - Low birth weight
- Increased perinatal morbidity and mortality in the mother and fetus correlate with the severity of pre-eclampsia, preterm delivery, multiple gestations, and preexisting maternal medical conditions
- Postdelivery liver biochemical test abnormalities generally resolve

HELLP syndrome

1- Definition:

- Hemolysis, elevated liver tests, and low platelets

2- Epidemiology

- More common in the **third trimester** (usually at or after 32 weeks but as early as 25 weeks); 15% to 25% of cases occur postpartum (most within 2 days of delivery but can be later)
- **Incidence:** 0.2% - 0.6% of all pregnancies; 4% - 12% in women with pre-eclampsia/eclampsia
- May occur in patients with AFLP or de novo
- **Risk factors:** white race, multiparity, age greater than 25 years

3- Etiology:

- Unknown. Pathogenic factors may include abnormal vascular tone, vasospasm, coagulation, and LCHAD deficiency in the infant

4- Clinical and laboratory features

- **Manifestations:**
  - Epigastric pain (65%), nausea or vomiting (30%), headache (31%), hypertension (85%),visual changes, weight gain, edema
- Microangiopathic **hemolytic anemia** with increased serum lactate dehydrogenase and indirect bilirubin levels and decreased haptoglobin levels
- Elevated serum **aminotransferase** levels (from mild to 10 - 100 times)
- **Decreased platelet count** (may be lower than 10,000/mm3)
- Proteinuria
- **Positive D-dimer test** is possibly predictive of HELLP syndrome in pre-eclamptic patients
- **Postpartum resolution of the following:**
  - Abnormal platelets, usually within the first 5 days
  - Hypertension or proteinuria, if present, up to 3 months

5- Diagnosis:

- Presence of hemolytic anemia, elevated serum aminotransferase levels, and low platelets

6- Treatment:

- **Delivery of the infant**:
  - Indicated in the presence of maternal or fetal distress or a rapidly dropping platelet count.
  - Coexisting pre-eclampsia or AFLP may dictate early delivery
- **Hospitalization** is indicated for treatment of hypertension, stabilization of DIC, seizure prophylaxis, and fetal monitoring
- **Corticosteroids**:
  - Recommended if gestation is < 34 weeks, to improve fetal lung maturity

- But the use of corticosteroids to improve postpartum maternal outcome remains experimental

7- Outcome:

- Maternal mortality rate of 1%
- Perinatal infant mortality rate of 7% to 22%
- **Complications to mother:**
  - Maternal DIC
  - Abruptio placentae
  - Eclampsia
  - Ascites
  - Subcapsular hematoma
  - Hepatic rupture
  - Wound hematoma
  - Renal, cardiopulmonary, or hepatic failure
- **Increased risk of infant:**
  - Prematurity
  - Intrauterine growth retardation
  - DIC
  - Thrombocytopenia

Hepatic rupture

1- Definition: Rupture of the hepatic capsule

2- Epidemiology

- Occurs in 1 in 45,000 to 1 in 250,0000 deliveries
- **Incidence:** 0.9% to 2% in patients with HELLP syndrome
- Most cases are associated with pre-eclampsia, eclampsia, AFLP, or HELLP
- Also occurs with hepatocellular carcinoma, adenoma, hemangioma, and hepatic abscess
- Recurrence is rare

3- Etiology:

- In **HELLP and pre-eclampsia/eclampsia**, hepatic rupture is usually preceded by severe intraparenchymal hepatic hemorrhage that progresses to subcapsular hematoma in patients with severe thrombocytopenia

4- Clinical and laboratory features:

- Usually occurs in last trimester or occasionally within 24 hours of delivery
- **Typical symptoms:**
  - Sudden onset of abdominal pain, nausea, and vomiting
  - Followed by abdominal distention and hypovolemic shock
  - Usually involves the right lobe of liver but may occur in either or both lobes
- **Serum aminotransferase levels** are increased 2 - 100 times and associated with anemia and consumptive thrombocytopenia, with or without DIC

5- Diagnosis:

- Abdominal U/S, CT, MRI, and angiography are useful

6- Treatment

- Early recognition leads to **prompt delivery** and surgical or radiologic intervention
- **Surgical therapies include:**
  - Application of direct pressure, evacuation, packing or hemostatic wrapping, topical hemostatic agents, oversewing lacerations, hepatic artery ligation, partial hepatectomy, and liver transplantation
- **Angiographic embolization** is an alternative option

7- Outcome

- Maternal mortality rate of 50% (caused by hemorrhagic shock, hepatic failure, cerebral hemorrhage)
- Fetal mortality rate of 10% - 60% (caused by placental rupture, prematurity, intrauterine asphyxia)

Approach to the pregnant patient

History

1- **Relation to time of gestation** [Differential diagnosis of elevated serum aminotransferase levels and/or jaundice according to trimester of pregnancy]

Trimester	**Differential diagnosis**
First	- Hyperemesis gravidarum - Gallstones - Viral hepatitis - Drug-induced hepatitis - Intrahepatic cholestasis of pregnancy*
Second	- Intrahepatic cholestasis of pregnancy - Gallstones - Viral hepatitis - Drug-induced hepatitis - Pre-eclampsia/eclampsia* - HELLP syndrome*
Third	- Intrahepatic cholestasis of pregnancy - Pre-eclampsia/eclampsia - HELLP syndrome - Acute fatty liver of pregnancy - Hepatic rupture - Gallstones - Viral hepatitis - Drug-induced hepatitis

*Uncommon in this trimester.
HELLP, hemolysis, elevated liver tests, low platelets

2- **Pruritus**

- Characteristic of IHCP
- Affects palms of hands and soles of feet initially, then elsewhere

3- **Nausea and vomiting**

- Occurs in 50% - 90% of all pregnancies
- Key feature of hyperemesis gravidarum
- When associated with headache and peripheral edema may indicate pre-eclampsia

- When associated in late pregnancy with abdominal pain, with or without hypotension, may indicate hepatic rupture

4- **Abdominal pain**

- The location, character, duration, and factors that induce or relieve pain should be noted
- Right upper quadrant or midabdominal pain in late pregnancy may have ominous implications. Consider:
    - Cholelithiasis
    - AFLP
    - Hepatic rupture
    - Pre-eclampsia

5- **Jaundice**

- Note the relation of jaundice to the onset of other symptoms
- Jaundice follows pruritus in IHCP

6- **Systemic symptoms**

- Headache, peripheral edema, foamy urine, oliguria, and neurologic symptoms may occur in pre-eclampsia
- Fever, malaise, and a change in stools may indicate infection such as hepatitis
- Easy bruisability may occur in HELLP syndrome
- Weight loss or gain or dizziness may occur with liver disease in pregnancy

7- **History of past pregnancy and birth control use**

- Note the time of onset of symptoms in previous pregnancies
- Note the outcome of previous pregnancies
- A history of jaundice with previous birth control use is a risk factor for IHCP

8- **Relevant pregnancy-related factors**

- Multiple versus single gestation
- Primiparous versus multiparous

- Medications

Rates of recurrence of pregnancy-associated liver disease in subsequent pregnancies

Disease	Rate of recurrence
Intrahepatic cholestasis of pregnancy	40%–70%
HELLP syndrome	4%–27%
Acute fatty liver of pregnancy	20%–70% in carriers of LCHAD* mutation
Pre-eclampsia	2%–43%

*LCHAD, long-chain 3-hydroxyacyl-coenzyme A dehydrogenase

Physical examination

1- **Normal findings** that occur in pregnancy include:

- Spider telangiectasias
- Palmar erythema

2- **Abnormal findings** that occur with liver disease in pregnancy are:

- Jaundice
- Hepatomegaly
- Hepatic tenderness
- Friction rub or bruit
- Splenomegaly
- Murphy's sign
- Diffuse excoriations

3- **Systemic findings** that may occur with liver disease in pregnancy are:

- Hypertension
- Orthostatic hypotension
- Peripheral edema
- Asterixis
- Hyperreflexia or other neurologic findings
- Ecchymoses, and petechiae

Diagnostic tests

1- **The only major restrictions** compared with the nongravid state are:

- Radiation and gadolinium exposures

2- **Routine** blood chemistry tests and a blood count are helpful

3- **Uric acid levels:**

  - Often elevated in AFLP
  - May be elevated in pre-eclampsia

4- **Features of HELLP syndrome:**

  - Hemolysis and a low platelet count
  - DIC with a low fibrinogen level, increased fibrin split products, and an elevated partial thromboplastin time may also occur

5- **Elevations in the serum bile acid level:**

  - Occur before or are concurrent with the onset of IHCP

6- **Amylase and lipase** levels should be checked in a patient with abdominal pain

7- **If viral hepatitis is suspected**, serologic tests should be checked for the following:

  - Hepatitis A (IgM and IgG antibody to hepatitis A virus [anti-HAV])
  - Hepatitis B ([HBsAg] and antibody, core antibody, and, if HBsAg is positive, e antigen and antibody)
  - Hepatitis C ([anti-HCV] and possibly HCV RNA).
  - If the patient has traveled to an endemic area, consider testing for hepatitis E

8- **Endoscopy, including ERCP:**

  - The benefits should be weighed against the risks in pregnancy.
  - Risks include fetal hypoxia from sedative drugs or positioning.
  - Sedative medications and radiation exposure should be minimized

9- **Abdominal U/S** is safe and useful

10- **Abdominal CT:**

  - Although it is more sensitive than U/S for hepatic rupture and may yield more information, radiation exposure and the stability of the patient should be considered in decisions about the choice of imaging test

11- **Angiography:**

  - Rarely needed for hepatic rupture

12- **MRI:**

- Probably safe, although this is not conclusively proven.
- Gadolinium should not be used in pregnancy

Results of laboratory tests in pregnancy-associated liver disease

	Aminotransferases*	Bile acids*	Bilirubin	ALP	Uric acid	PLT	PT/PTT	Urine protein
Hyperemesis Gravidarum	1–2×	Normal	<5 mg/dL	1–2×	Normal	Normal	Normal	Normal
Intrahepatic cholestasis of pregnancy	1–4×	30–100×	<5 mg/dL	1–2×	Normal	Normal	Normal	Normal
Acute fatty liver of pregnancy	1–5×	Normal	<10 mg/dL	1–2×	↑	± ↓	± ↑	± ↑
Pre-eclampsia/ Eclampsia	1–100×	Normal	<5 mg/dL	1–2×	↑	± ↓	±↑	↑
HELLP Syndrome	1–100×	Normal	<5 mg/dL	1–2×	↑	↓	±↑	± ↑
Hepatic Rupture	2–100×	Normal	±↑	↑	Normal	± ↓	± ↑	Normal

*Results are indicated as times the upper limit of normal.

Pregnancy in patients with chronic liver disease

Overview

1- Patients have more difficulty conceiving

2- Pregnancy has no adverse effect on the progression of liver disease

Cirrhosis

1- The risk of bleeding esophageal varices is increased (more commonly in the second and third trimesters).

- Etiology:
  - Expanded maternal blood volume
  - Fetal compression of maternal inferior vena cava
  - Collateral vasculature
- Risk of esophageal bleeding

- Cirrhosis: 18% to 32%
- Known portal hypertension: 50%
- Preexisting varices: 78%

- Treatment:
    - The same as in a nongravid patient and includes band ligation or sclerotherapy and, if necessary, TIPS or portosystemic shunt surgery
    - Screening endoscopy is recommended in patients with cirrhosis before pregnancy or early in the second trimester
    - Areas of controversy include the delivery method (elective caesarian section to avoid Valsalva maneuver during vaginal birth?) and primary prophylaxis of variceal bleeding with banding or beta blockers
- Outcome
    - Maternal mortality rate of 18% to 50%

2- **Other complications** of cirrhosis in pregnancy:

- Hepatic decompensation (24%)
- Splenic artery anurysm rupture (2.6%)
- Postpartum uterine hemorrhage (7% to 10%)
- Spontaneous abortion (30% to 40%)
- Prematurity (25%)
- Fetal stillbirth (13%)
- Neonatal mortality (4.8%).

3- **Medications:**

- Should be reviewed carefully for safety in pregnancy
- Furosemide, spironolactone, beta blockers, fluoroquinolones, and rifaximin → are pregnancy category C drugs
- Octreotide and lactulose → are FDA category B drugs.

Wilson disease

1- **Impact on pregnancy:**

- The disease may decrease fertility and increases the rate of recurrent spontaneous abortions

2- **Treatment:**

- Pregnant patients should **continue anticopper therapy** (penicillamine, trientine, zinc) during pregnancy because serious adverse maternal outcomes, including death, can result if anticopper therapy is stopped
- Data in pregnancy are limited for all three anticopper drugs
- Penicillamine is potentially teratogenic in animals and humans. Trientine is teratogenic in animals
- Penicillamine is considered safe during pregnancy at relatively low doses (0.25 to 0.5 g/day).
- Trientine has appeared safe and effective based on limited data.
- Because of the potential teratogenic effects of penicillamine and trientine, **zinc is recommended** during pregnancy by some authorities

3- **Special considerations:**

- Genetic counseling should be offered

Autoimmune hepatitis

1- **Impact on pregnancy**

- The natural history of AIH is variable during pregnancy
- Successful pregnancies can occur in women with well-controlled AIH
- The rate of fetal loss is 19% - 24% (no different from that for other chronic diseases)

2- **Treatment**

- Cessation of therapy during pregnancy is associated with **relapse** of disease

- The use of azathioprine is controversial, but reports of experience in patients taking azathioprine following organ transplants or for inflammatory bowel disease have described good outcomes for mothers and infants
- Patients should be monitored closely for flare-ups of AIH during pregnancy and in the early postpartum period

3- **Special considerations:**

- Women of childbearing age with AIH should be counseled to consider pregnancy only if the disease is well-controlled

Primary biliary cirrhosis

1- **Impact on pregnancy**

- Some data suggest that women with primary biliary cirrhosis may be able to have normal pregnancies
- Antimitochondrial antibody titers and serum alkaline phosphatase, ALT, bile acid, bilirubin, and IgG and IgM levels improve during pregnancy
- The risk of postpartum flare-up exists

2- **Treatment:**

- Continue UDCA, which is safe in pregnancy

Primary sclerosing cholangitis

1- **Impact on pregnancy:**

- The natural history in pregnancy is unknown

2- **Treatment:**

- Continue UDCA, which is safe in pregnancy, improves maternal symptoms, and decreases the risk of fetal complications

Viral hepatitis

1- **Overview**

- Of all the viral hepatitides, only the course of hepatitis E is affected by pregnancy
- Viral hepatitis may occur throughout pregnancy

2- **Hepatitis A**

- Epidemiology
    - This occurs in as many as 1 in 1000 pregnancies in the United States
    - Perinatal transmission is rare
    - Acute infection only occurs (no chronic disease)
- Treatment
    - The course and management are unaffected by pregnancy
    - Prevention with immune globulin in an exposed mother is safe for mother and fetus
    - For infants of mothers infectious at or soon after delivery, the dose of immune globulin is 0.02 mL/kg intramuscularly (vaccination against HAV can be considered at age 2 years)

3- Hepatitis B

- Epidemiology
    - Acute disease occurs in 2 of 1000 pregnancies
    - Chronic disease occurs in 5 to 15 per 1000 pregnancies in the United States
- Transmission to the infant may occur without immunoprophylaxis
    - When the mother is HBsAg positive and HBeAg negative, the chronic infection rate is 40%
    - When the mother is HBsAg and HBeAg positive, the chronic infection rate is 90%
    - The risk of transmission to the infant correlates with the mother's serum HBV DNA level
    - Following infection of the mother in the first trimester, 10% of neonates become HBsAg positive
    - Following infection of the mother in the third trimester, 80% to 90% of neonates become HBsAg positive
    - Transmission to the neonate is usually perinatal
- Treatment:

- A combination of active (HBV vaccine) and passive (hepatitis B immune globulin) immunotherapy of the newborn is 85% to 95% effective in decreasing perinatal transmission to less than 10%
- For treatment of HBV see chronic hepatitis ®

Treatment of neonates born to mothers with hepatitis B

Treatment	**Age of administration to infant based on hepatitis B surface antigen status of mother**		
	+	**Unknown**	–
Hepatitis B immune globulin 100 IU (0.5 mL IM)	≤12 hr	≤12 hr	Not administered
Hepatitis B vaccine, first dose 5.0 µg (0.5 mL IM)	≤12 hr	≤12 hr	≤1 wk
Subsequent hepatitis B vaccine doses: - Recombivax HB 5 µg (0.5 mL)	1 mo	1–2 mo	1–2 mo
- Engerix-B 10 µg (0.5 mL)	6 mo	6 mo	6–18 mo

4- Hepatitis C

- Epidemiology
  - The overall rate of mother-to-infant transmission is generally low (4% to 10%). Higher rates of vertical transmission are reported when maternal viral titers are high (36% when the maternal serum HCV RNA level is higher than 1010 copies/mL) and with human immunodeficiency virus coinfection
  - HCV infection does not adversely affect pregnancy
  - The course of HCV infection is not affected by pregnancy
- Treatment
  - No effective prevention is available for infants

    - Treatment of chronic hepatitis C with pegylated interferon and ribavirin is **contraindicated** in pregnancy because ribavirin is teratogenic

5- Hepatitis D

- Rare instances of vertical transmission have been reported
- Hepatitis B infection should be controlled to prevent the spread of hepatitis D virus

6- Hepatitis E

- **Jaundice** is nine times more common in pregnant than nonpregnant women with hepatitis E
- Hepatitis E is the leading cause of **fulminant hepatic failure** in pregnancy
- The disease is more severe in the **third trimester** than at other times, with a maternal mortality rate of up to 27%, compared with 0.5% to 4% in nonpregnant patients.
- In patients with fulminant hepatic failure, the mortality rate is 65% in pregnant women compared with 23% in nonpregnant women
- The risk of abortion and intrauterine death is 12%
- Vertical transmission occurs in up to 33%
- No specific therapy during pregnancy exists

7- HSV infection

- Disseminated HSV infection during pregnancy is **rare**, but it has been reported, usually in the late second or third trimester
- The clinical presentation can include **fulminant hepatitis**
- Features:
    - Fever
    - Nausea, vomiting, abdominal pain
    - Leukopenia, thrombocytopenia, coagulopathy

    - Markedly elevated serum aminotransferase levels are often present
- **Liver biopsy** specimens show extensive necrosis, often hemorrhagic, with typical intranuclear viral inclusion particles
- Hepatic necrosis, DIC, hypotension, and death can occur rapidly if antiviral therapy is not initiated promptly

Budd-Chiari syndrome

1- Definition:

- Thrombosis of one or more of the three hepatic veins

2- Epidemiology

- 20% of cases are associated with pregnancy and oral contraceptive use
- Postpartum onset is rare and is associated with a poor prognosis

3- Etiology

- A hypercoagulable state (e.g., factor V Leiden mutation) may play a role
- It may be associated with antiphospholipid antibodies, pre-eclampsia, and ingestion of herbal teas

4- Clinical features

- Symptoms are usually acute in pregnancy
- Features include abdominal pain, hepatomegaly, and ascites

5- Diagnosis

- MRI, ultrasonography, and liver biopsy are used
- If possible, venography or angiography should be avoided until after pregnancy

6- Treatment:

- Same as in nonpregnant patients

7- Outcome:

- With acute onset in pregnancy, the maternal mortality rate is as high as 70%.

Cholelithiasis and Cholecystitis

1- Epidemiology

- Onset:
  - Symptomatic onset is most common in the second and third trimesters
- The frequency in pregnancy:
  - 18% to 19% in multiparous women and 7% to 8% in primiparous women.
  - Symptomatic gallstones occur only in 0.1% to 0.3% of pregnancies
- Risk factors include:
  - Increasing age, increasing frequency and number of pregnancies
  - Obesity, high serum leptin levels, insulin resistance, and low high-density lipoprotein levels
- Frequency rates of new biliary sludge and gallstones in pregnancy are:
  - 14% and 2%, respectively, at the end of the second trimester
  - 31% and 2%, respectively, 2 to 4 weeks postpartum
- Sludge disappears in 61% of patients at 3 months and in 96% at 12 months after delivery; gallbladder stones disappear in 13% to 28% of women by 1 year

2- Etiology

- Increased estrogen levels lead to increased lithogenicity of bile in the second and third trimesters (increased cholesterol secretion and supersaturation of bile)
- Increased progesterone levels lead to larger gallbladder volume and decreased emptying time

3- Clinical features

- Vomiting occurs in 32%, dyspepsia in 28%, and pruritus in 10%

- Biliary pain occurs in 29% with preexisting stones and in 4.7% with sludge but generally does not occur in patients with new sludge or stones

4- Treatment

- Conservative medical management:
  - Intravenous fluids
  - Correction of electrolytes
  - Bowel rest
  - Broad-spectrum antibiotics
- Laparoscopic cholecystectomy:
  - Should be performed in the **second trimester** if medical management fails or the patient has a relapse.
- Surgery should be avoided in the first trimester if possible
  - A questionable increase in spontaneous abortions occurs when surgery is performed in the first trimester
  - Surgery in the third trimester is associated with premature labor in 40% of cases
- ERCP should be done for choledocholithiasis
  - It can be performed safely by shielding the fetus from radiation exposure and minimizing fluoroscopy time

Hepatobiliary complications of HIV

Viral hepatitis and other viral infections

Hepatitis A virus

1- **Seroprevalence** of antibody to HAV:
  - Is high among HIV-infected persons, with a range of 40% - 70%.

2- **The annual cumulative incidence** of HAV infection:
  - Is reported to be 5.8% per year among HIV-positive persons

3- **HAV viremia:**
  - Is prolonged in HIV-infected persons
  - The level of HAV viremia is higher compared with those without HIV infection, even with relatively high CD4+ T lymphocyte counts

4- **Effect of ART:**
  - No evidence indicates a detrimental effect on the course of HAV infection

5- **Hepatitis A vaccination:**

- Recommended for all HIV-positive/HAV-seronegative persons
- Standard doses given 6 - 12 months apart.
- Immune response is excellent (overall response rate, 78% - 94%), even in persons with CD4+ counts < 200 cells/mm3 (response rate, 64%).

Hepatitis B and D viruses

1- Prevalence:

- Worldwide, 10% of HIV-infected persons are chronically infected with HBV

2- HIV adversely affects the natural history of HBV infection.

- Compared with those infected with HBV alone, HIV-coinfected persons have a higher rate of progression from acute to chronic HBV
- Higher HBV DNA levels
- Lower rates of spontaneous hepatitis B e antigen (HBeAg) to antibody to HBeAg (anti-HBe) seroconversion
- Increased frequency of reactivation episodes
- Faster progression to hepatic cirrhosis
- Earlier development of and more aggressive hepatocellular carcinomas

3- HIV/HDV coinfection :

- May accelerate progression of hepatitis D virus (HDV)–associated liver disease

4- Indication of treatment:

- All HIV/HBV-coinfected patients with active HBV replication should be considered for HBV antiviral therapy, which can potentially prevent development of liver-related complications and reduce HBV transmission

5- The goals of HBV treatment in HIV-infected persons are:

- Suppression of HBV DNA to an undetectable level (as for persons without HIV infection)
- Return of serum aminotransferase levels to normal

- HBeAg seroconversion (not applicable to HBeAg negative–pre-core/core promoter mutant states
- Improvement in liver histology

6- **Antiviral medications:**

- Seven antiviral medications have been approved in the United States for chronic HBV treatment
- Three of these have also been approved for HIV treatment.
- The choice of therapy for HBV infection depends on the need for HIV treatment

Antiviral medications for chronic hepatitis B
1- Interferon alfa-2b 2- Peginterferon alfa-2a 3- Lamivudine* 4- Adefovir 5- Entecavir 6- Telbivudine 7- Tenofovir*

*Also approved to treat HIV infection.

*Tenofovir is also available in combination with emtricitabine (Truvada®).

7- **When both HIV and HBV infections meet criteria for treatment**:

- Combination oral nucleoside/nucleotide analogue therapy with tenofovir 300 mg daily plus either emtri citabine 200 mg daily or lamivudine 300 mg daily is preferred.
- Because replication of both viruses depends on reverse transcription, dual HIV/HBV therapy can use the same reverse transcriptase-inhibiting agents to treat both viruses

8- **When HBV infection requires treatment but HIV infection does not**:

- Medications with no capacity to induce HIV-resistance mutations, such as subcutaneous peginterferon alfa-2a or oral adefovir (10 mg daily), can be used
- Antiviral therapy that includes tenofovir plus emtricitabine (or lamivudine) is an option
- Entecavir in the absence of ART can reduce HIV RNA levels and select for HIVresistance mutations, so it should not be used in an HIV-infected person without ART.
- Telbivudine does not have intrinsic activity against HIV in vitro, but it has been associated with declines in HIV RNA levels and can select for lamivudine-resistance mutations. It is not a recommended treatment for the HIV/HBV-coinfected patient at present

9- **Peginterferon alfa-2a :**

- Frequent toxicities and low rates of therapeutic success have limited its use as HBV therapy in HIV-infected persons
- But it may be effective for HBeAg-positive persons with elevated serum aminotransferase levels and low HBV DNA levels

10- **Lamivudine resistance:**

- Because lamivudine resistance occurs at a rate of 15% - 25% per year, lamivudine resistance may be present in HIV-infected patients who previously received lamivudine as part of an ART regimen.
- However, tenofovir remains active in patients with lamivudine resistant HBV infection and can suppress HBV DNA to undetectable levels, because of the potency of tenofovir and the lack of cross-resistance between lamivudine and tenofovir

11- **For patients receiving combination** tenofovir plus emtricitabine (or lamivudine) who fail to suppress HBV DNA by 24 - 48 weeks:

- Adding entecavir 1 mg daily may be considered

12- **Screening for HCC:**

- Abdominal U/S and alpha fetoprotein testing is recommended every 6 - 12 months

13- **HBV vaccination:**

- Recommended in all HIV-positive/HBV surface antibody (anti-HBs) – negative persons.
- The presence in serum of isolated hepatitis B core antibody (anti-HBc) with no other HBV markers most likely reflects previous exposure and recovery, rather than a false-positive test, but not necessarily

14- **Anti-HBs titers should be evaluated** after HBV vaccination in HIV-infected persons.

- Immune reactivity to the HBV vaccine is frequently suboptimal in these persons in terms of rate of response, antibody titers, and durability.
- A CD4+ count > 500 cells/ mm3 and an HIV viral load < 1000 copies/mL promote optimal vaccine responses.
- Revaccination should be instituted if the anti-HBs titer < 10 IU/L

Hepatitis C virus

1- **Prevalence:**

- Among HIV-infected persons, 30% are chronically coinfected with hepatitis C virus (HCV)

2- **The natural history of HCV infection is adversely influenced** by HIV coinfection:

- Compared with persons infected with HCV alone, HIV-coinfected persons more commonly progress to chronic HCV
- Have higher HCV RNA levels
- Are at higher risk of cirrhosis, hepatic decompensation, and liver-related death
- Have a shorter survival once end-stage liver disease develops

- HCV-related liver disease is now a leading cause of death in the HIV-infected population
- HIV/HCV coinfection increases the risk of HCC compared with HIV monoinfection persons but not HCV monoinfection

3- **Effect of ART:**

- Available data suggest that ART favorably affects the course of HIV disease in HIVinfected patients, decreases mortality from liver disease, and should not be withheld from HIV/HCV-coinfected persons on account of potential toxicity

4- **The stage of hepatic fibrosis**:

- Can help guide HCV treatment decisions in HIV/HCV patients.
- The incidence rate of hepatic decompensation events or death is higher in coinfected patients with more advanced fibrosis at the time of staging

5- **The timing of HCV therapy:**

- Depends on the need for HIV treatment.
- HCV treatment should be considered first if liver disease is advanced and HIV infection is at an early stage.
- If HIV infection requires treatment, ART should be initiated first, and once the HIV infection is controlled, HCV therapy can be considered

6- **Indication of treatment:**

- All coinfected patients who do not have decompensated cirrhosis or other contraindications.

7- **Treatment regimen:**

- Peginterferon alfa-2a plus ribavirin for 48 weeks (regardless of HCV genotype) is the standard of care for treating chronic HCV infection in the setting of HIV infection.

8- **The main goals of treatment are:**

- Viral eradication (i.e., sustained virologic response)
- Reduction in the risk of liverrelated complications

9- **Response to treatment:**

- Weight-based ribavirin (1000 mg daily if body weight ≤ 75 kg and 1200 mg if body weight > 75 kg) in combination with peginterferon alfa-2a can achieve sustained virologic response in up to 72% of HIV-infected HCV genotype 2 or 3 patients and in up to 35% of HIV-infected HCV genotype 1 or 4 patients.
- Most clinical trials have used a lower dose of ribavirin (800 mg daily), but increased response rates can be expected with weight-based ribavirin.

10- **Avoid zidovudine**:

- Which likely inhibits the hematopoietic response to ribavirin-induced hemolysis and is associated with greater declines in the hemoglobin level during HCV therapy
- Consider switching to an alternative nucleoside analogue before starting HCV treatment

11- **Avoid didanosine**:

- Which increases the risk of hepatic decompensation when used in conjunction with ribavirin and should not be administered during HCV therapy

12- **Abacavir and ribavirin:**

- Because abacavir and ribavirin are both guanosine analogues, abacavir may compete intracellularly with ribavirin and interfere with the effect of the drug on HCV.
- However, with weight-based ribavirin, use of abacavir (or other ART) is not associated with a reduced early or sustained virologic response, a finding that suggests that any competitive effect between abacavir and ribavirin can be overcome with optimal weight-based ribavirin dosing.
- Abacavir can therefore be continued in HIV/HCV-coinfected patients during HCV therapy

13- **Some adverse effects of HCV therapy** are more prominent in the HIV/HCV-infected population.

  - Pegylated interferon can reduce absolute CD4+ cell counts during treatment, although the percentage of CD4+ cells is typically unchanged.
  - Weight loss is more common among HIV/HCV-coinfected than HCV-monoinfected patients during HCV therapy

14- **Maintenance pegylated interferon monotherapy**:

  - Does not slow progression of hepatic fibrosis among HIV/HCV-infected nonresponders to pegylated interferon alpha plus ribavirin

Other viruses

1- **Acute infection with HIV:**

  - May manifest with hepatitis as part of a mononucleosis-like illness:
    - Fever, malaise, and myalgias
    - Hepatosplenomegaly
    - Elevations of serum aminotransferase and alkaline phosphatase levels.
  - This presentation is referred to as the **acute retroviral syndrome**

2- **Several other common viral infections** can secondarily affect the liver and cause acute hepatitis.

  - Adenovirus, Epstein-Barr virus, cytomegalovirus, herpes simplex virus, and varicellazoster virus are rare causes of acute viral hepatitis in HIV-infected persons

Other infections

Disseminated mycobacterium avium complex infection

1- **The designation MAC:**

  - Refers to infections caused by one of two nontuberculous mycobacterial species, either *Mycobacterium avium* or *M. intracellulare*

2- **Presentation with AIDS:**

  - Usually presents as disseminated disease and may involve the liver

3- **Symptoms and signs of disseminated MAC infection include:**

  - Fever, night sweats
  - Abdominal pain (especially in the right upper quadrant)
  - Diarrhea
  - Weight loss.
  - May be hepatosplenomegaly

4- **Laboratory abnormalities** frequently include:

  - Anemia
  - Elevated serum alkaline phosphatase and LDH levels

5- **The diagnosis may be confirmed by the following:**

  - Isolation of MAC from cultures of blood, lymph node, or bone marrow
  - Histopathologic findings on a liver biopsy specimen showing granulomas with positive acid-fast bacilli stains
  - Mycobacterial growth from culture of liver tissue obtained by biopsy

Peliosis hepatis

1- **Definition and etiology:**

  - Vascular proliferative hepatic infection in HIVinfected persons with advanced immunosuppression that is characterized by multiple bloodfilled cystic spaces
  - Caused by Bartonella henselae

2- **Manifestations:**

  - May be fever, abdominal pain, nausea, vomiting, anorexia, and weight loss.
  - May be hepatosplenomegaly

3- **Laboratory findings:**
   - Increased serum alkaline phosphatase levels and thrombocytopenia or pancytopenia may be identified

4- **Abdominal CT:**
   - Typically shows hepatosplenomegaly and hypodense lesions scattered throughout the hepatic parenchyma

5- **Positive Bartonella serology**:
   - Can be used as supportive information in the appropriate clinical setting

6- **The diagnosis is confirmed by:**
   - Isolation of Bartonella from cultures of blood or liver tissue
   - Or by Warthin-Starry staining of a biopsy specimen

7- **Treatment:**
   - Oral erythromycin 500 mg 4 times daily or doxycycline 100 mg twice daily for 4 months is the recommended therapy
   - Oral azithromycin 500 mg daily or clarithromycin 500 mg twice daily for 4 months may be an option for patients who cannot tolerate erythromycin or doxycycline

Fungal and protozoal infections

1- A number of **fungi and protozoa** may infiltrate the liver in patients with AIDS, usually as part of disseminated disease

Selected causes of liver disease in HIV-infected patients

Bacteria	- Mycobacterium avium complex - Mycobacterium tuberculosis - Bartonella henselae (peliosis hepatis)
Viruses	- Hepatitis A virus - Hepatitis B virus - Hepatitis C virus - Hepatitis D virus (with hepatitis B) - Other: adenovirus, Epstein-Barr virus, cytomegalovirus, human immunodeficiency virus, herpes simplex virus, - varicella-zoster virus
Fungi	- Candida albicans

	- Coccidioides immitis - Cryptococcus neoformans - Histoplasma capsulatum - Sporothrix schenckii - Penicillium marneffei - Pneumocystis jirovecii
Protozoa	- Microsporidia spp - Schistosoma spp. - Toxoplasma gondii
Malignant diseases	- Hepatocellular carcinoma - Lymphoma - Kaposi's sarcoma - *Nonalcoholic fatty liver disease*
Medications and toxins	- Acetaminophen - Alcohol - Nucleoside analogues: didanosine, stavudine, zidovudine - Non-nucleoside reverse transcriptase inhibitors: nevirapine - Antituberculosis drugs: isoniazid, rifampin - Antimicrobials: macrolides, trimethoprim-sulfamethoxazole

Malignant diseases

Lymphoma

1- **Prevalence:**

- Non-Hodgkin's lymphoma accounts for most systemic AIDS-related lymphomas
- The liver is involved in approximately 1/3 of cases

2- **Manifestations:**

- May be clinically silent
- Or associated with pain and "B" symptoms, including fever, weight loss, and night sweats.
- Jaundice may occur with intrahepatic or extrahepatic bile duct obstruction

3- **Diagnosis:**

- Radiographic imaging usually reveals solitary or multiple hepatic lesions and involvement of abdominal lymph nodes
- Biopsy of the hepatic lesions or an involved lymph node confirm the diagnosis

Kaposi's sarcoma

1- **Risk factors:**

- This is observed predominantly in men who have sex with men

2- **Features:**

- Typically, it involves the liver in the setting of cutaneous disease.
- ± Abdominal pain, hepatomegaly
- ± Elevations of serum alkaline phosphatase levels

3- **Diagnosis:**

- Abdominal U/S → may reveal nonspecific, small (5- to 12-mm) hyperechoic nodules.
- CT of the liver → may show enhancing lesions in capsular, hilar, and portal areas with invasion into liver parenchyma

Hepatocellular carcinoma

1- **Risk factors:**

- Recognized in HIV-infected patients with cirrhosis
- It may occur in the setting of chronic HBV infection in the absence of cirrhosis

2- **Features:**

- Patients typically have evidence of advanced liver disease

- May have an elevated serum alpha fetoprotein level and one or more liver masses on abdominal imaging studies

Nonalcoholic fatty liver disease

1- **Prevalence:**
  - Macrovesicular hepatic steatosis is a common histologic finding in patients coinfected with HIV and HCV and is identified in 40% - 69% of liver biopsy specimens

2- **Risk factors for hepatic steatosis** among HIV/HCV-coinfected patients have included:
  - White race
  - Increased body mass index
  - Hyperglycemia
  - Use of dideoxynucleoside analogues (i.e., didanosine and stavudine),
  - Lower plasma levels of high-density lipoprotein cholesterol
  - The frequency of hepatic steatosis among HIV/HBV-coinfected persons and HIVmonoinfected persons remains unclear

3- **Sequlae:**
  - Steatosis/steatohepatitis has been associated with more advanced HCV-related hepatic fibrosis in HIV-infected persons

4- **Manifestations:**
  - Most patients are asymptomatic.
  - Hepatomegaly is a frequent finding

5- **Diagnosis:**
  - Elevated serum aminotransferase or alkaline phosphatase levels may be identified.
  - Evidence of fatty liver may be noted on abdominal U/S or CT

Antiretroviral induced hepatotoxicity

1- **Effect of ART:**

  - Virtually every ART has been associated with elevations in liver biochemical test levels

2- **Four main mechanisms of ART-related hepatotoxicity** occur in HIV-infected persons:

  - Mitochondrial toxicity
  - Hypersensitivity reactions involving the liver
  - Direct drug toxicity
  - Immune reconstitution following initiation of ART in the presence of hepatitis coinfection

3- **Manifestations:**

  - No clinical finding is specific for ART-induced hepatotoxicity.
  - Symptoms may be absent or may consist of abdominal discomfort, nausea, rash, anorexia, jaundice, or fever

4- **Diagnosis**:

  - Hepatotoxicity is usually suggested by elevations in serum aminotransferase levels.
  - Cholestasis is less frequent
  - Some cases are characterized by mixed hepatitis and cholestasis

5- Based on the AIDS Clinical Trial Group liver toxicity scale, severe **hepatotoxicity is defined as either:**

  - Grade 3 (5.1 - 10 times the upper limit of normal) Or grade 4 (> 10 times the upper limit of normal) change in serum aminotransferase levels during ART
  - Or a more than 3.5-fold increase in these levels above baseline if aminotransferase levels are elevated at initiation of ART

6- **Risk factors:**

  - HBV infection and HCV infection increase the risk of ART-associated hepatotoxicity, and the risk among HIV/HCV-coinfected patients with advanced fibrosis or cirrhosis is increased further. Eradication of HCV with antiviral therapy has been shown to improve tolerance to ART

- Patients with aminotransferase elevations before the initiation of ART have an increased risk of hepatotoxicity.
- Alcohol and cocaine use can exacerbate ART-induced hepatotoxicity

7- **Discontinuation of ART medications** should be considered in the following circumstances:

  - Serum aminotransferase levels exceed 10 times the upper limit of normal
  - Overt jaundice with elevated direct bilirubin levels is identified
  - Symptomatic hepatitis develops (increased risk of severe liver injury)
  - Findings consistent with drug hypersensitivity (e.g., rash, fever, eosinophilia) are observed

AIDS related biliary tract diseases

AIDS cholangiopathy

1- **Definition:**

  - This syndrome of biliary obstruction resulting from infection-associated strictures of the biliary tract is typically seen in patients with a CD4+ cell count < 100/mm3

2- **Incidence:**

  - Has declined substantially with the use of ART

3- **Etiology:**

  - Cryptosporidium parvum is the most common pathogen associated with AIDS cholangiopathy
  - But MAC, cytomegalovirus, Microsporidia spp., and Cyclospora cayatensis have also been identified.
  - Noninfectious causes include lymphoma or Kaposi's sarcoma infiltrating the biliary tree.
  - No specific cause is found in 20% - 40% of cases

4- **Manifestations:**

- This condition should be suspected in patients:
    - With advanced immunosuppression (CD4+ count < 100/mm3)
    - Who present with fever, right upper quadrant or epigastric abdominal pain, nausea, vomiting, diarrhea, jaundice, and hepatomegaly.
- The severity of abdominal pain varies with the biliary tract lesion:
    - Severe abdominal pain usually suggests papillary stenosis
    - Milder abdominal pain is often associated with intrahepatic and extrahepatic sclerosing cholangitis without papillary stenosis

5- **Laboratory:**

- Serum aminotransferase, alkaline phosphatase, and total bilirubin levels are typically mildly elevated
- But 20% of patients may have normal liver biochemical test levels

6- **Imaging:**

- Radiographic imaging may demonstrate intrahepatic or extrahepatic biliary tract dilatation or thickening of the bile duct
- ERCP is the preferred approach because it may be diagnostic (ampullary biopsy) or therapeutic (sphincterotomy). Cholangiography reveals one of four patterns:
    - Sclerosing cholangitis and papillary stenosis (most common)
    - Sclerosing cholangitis alone
    - Papillary stenosis alone
    - Long, extrahepatic bile duct strictures with or without sclerosing cholangitis

7- **Treatment:**

- Treatment is primarily endoscopic; the approach varies with the anatomic abnormality:
    - Papillary stenosis: Consider sphincterotomy

        - Isolated or dominant bile duct stricture: Consider endoscopic stenting
        - Isolated intrahepatic sclerosing cholangitis: Consider ursodeoxycholic acid 300 mg 3 times daily
    - Empiric antimicrobial therapy directed against typical pathogens (e.g., *C. parvum*):
        - Does not affect symptoms or cholangiographic abnormalities

Acalculous cholecystitis

1- This may occur in patients with **AIDS cholangiopathy**

2- Etiology:

- Typical causes include cytomegalovirus, C. parvum, Microsporidia spp., and Isospora belli.
- Less common causes are Candida albicans, Klebsiella pneumoniae, Salmonella typhimurium, and Pseudomonas aeruginosa

3- Presentation:

- May be similar to that of calculous cholecystitis, with severe right upper quadrant pain, fever, and Murphy's sign.
- Critically ill patients may present with unexplained fever or vague abdominal discomfort
- Physical examination may reveal a palpable right upper quadrant mass and jaundice (20%).

4- Laboratory:

- Leukocytosis, hyperbilirubinemia, and elevations in serum alkaline phosphatase and aminotransferase levels may be observed

5- Imaging:

- Abdominal U/S may demonstrate a thickened (> 3 - 4 mm) gallbladder wall, pericholecystic fluid, stones, or ductal abnormalities.
- In stable patients in whom the diagnosis is unclear after U/S, cholescintigraphy with a hepatobiliary iminodiacetic acid (HIDA) scan

may be useful. The diagnosis is confirmed by demonstrating failure of the gallbladder to opacify

6- **Prophylactic antibiotics:**

- Once acalculous cholecystitis is established, secondary infection with enteric pathogens is common.
- After blood cultures are obtained, broad-spectrum antibiotics (e.g., piperacillintazobactam, ampicillin-sulbactam, third-generation cephalosporin with metronidazole, or imipenem) should be initiated.
- Antibiotic therapy can be narrowed after microbiologic diagnosis

7- **Definitive therapy:**

- Cholecystectomy.
- If surgical intervention is contraindicated, consider drainage of the gallbladder through percutaneous cholecystostomy

The liver in heart failure

Etiology

Disease of the heart	**Effect on the liver**
Left and right ventricular failure (often coexist)	Hepatic congestion
Acute myocardial infarction with arrhythmia and cardiogenic shock which can complicate coronary artery disease	Ischemic hepatitis superimposed on the chronic hepatic congestion
Rheumatic heart disease, with mitral stenosis and tricuspid regurgitation	Severe hepatic congestion
The abrupt onset of atrial fibrillation or the development of bacterial endocarditis	Decrease left ventricular output and can aggravate hypoxic liver damage
Children with hypoplastic left heart syndrome and coarctation of the aorta	Hepatic necrosis, possibly because of the combination of reduced systemic blood flow, a left-to-right shunt, and markedly elevated right ventricular pressure
Drugs as amiodarone	Steatosis and fibrosis which may rarely progress to cirrhosis

Conditions that cause both liver disease and heart failure

1- Excess alcohol consumption
2- Hemochromatosis
3- Hepatitis C
4- The metabolic syndrome
5- Infiltrative diseases such as amyloidosis
6- Vascular tumors of the liver such as hemangioendothelioma

Causes of cardiac hepatopathy

Cause	**Percentage of total (%)**
Cardiomyopathy	49
Valvular disease	23
Pericardial disease	17
Pulmonary disease	9
Mixed causes	2

Frequency

1- Liver involvement is **common** in severe heart failure

2- A significant, albeit weak, **correlation** exists between the aminotransferase levels and both the right atrial pressure and the cardiac index

3- In patients with a **cardiac index > 2** L/minute/m2:

  - Only 20% - 30% of patients have minor elevations of serum liver enzyme levels.

4- In contrast, in those with a **cardiac index < 1.5** L/minute/m2:

  - Up to 80% of patients have major liver biochemical abnormalities

Clinical features

Congestive hepatopathy

1- **Symptoms and signs of right-sided heart failure:**

  - Dominated rather than those of liver disease in most patients

2- **Stigmata of liver disease:**

  - Such as palmar erythema, spider telangiectasias and caput medusae are rare, unless the liver disease and heart failure have a common cause, such as hemochromatosis

3- **Right upper quadrant pain:**

  - Results from stretching of the liver capsule and is mediated by the phrenic nerve

4- **Liver size:**

  - Can return to normal size as fibrosis develops during the course of severe hepatic congestion, but it is never reduced in size

5- **Jaundice**

  - Mild jaundice is common, but deep icterus is rare
  - Jaundice increases with prolonged and repeated bouts of heart failure
  - Hyperbilirubinemia may be in part unconjugated, related to infarcts of tissues, especially pulmonary infarcts.
  - Jaundice may then be prolonged, with conjugated hyperbilirubinemia because of the inability of the hypoxic liver to handle the bilirubin load

6- **Palpable systolic pulsation over the liver:**

  - Present in patients with tricuspid regurgitation (related to the transmission of right atrial pressure to the hepatic vein)

7- **Splenomegaly:**

- Frequent
- But, other features of portal hypertension are usually absent, except in severe cardiac cirrhosis associated with constrictive pericarditis

8- **Ascites:**

- Most likely related to increased sinusoidal pressure and permeability and increased leakage of lymph, rather than cirrhosis.
- As a result, the ascitic protein content is high (2.5 g/dL or higher), with a high serum-ascites albumin gradient (1.1 g/dL or higher).

9- **Peripheral edema and pleural effusions:**

- Probably reflect the cardiac disease, rather than the concomitant hepatic congestion

Characteristics of patients with cardiac hepatopathy

Characteristic	Acute heart failure (% of total)	Chronic heart failure (% of total)
Hepatomegaly	83	76
Jaundice	50	11
Ascites	42	68
Encephalopathy	25	2
Splenomegaly	8	15
Esophageal varices	0	8

Ischemic hepatitis

1- **Definition**

- This term refers to diffuse hepatic injury as a result of acute hypoperfusion
- The term *ischemic hepatitis* is a misnomer, because liver injury is characterized by centrilobular necrosis without inflammation

2- **Shock state:**

- Ischemic hepatitis as a result of low cardiac output may not be clinically obvious.

- A “shock” state is observed in only 50% of cases, and hypotension is not always documented; therefore, the left-sided heart failure may be subtle

3- **Usually, no specific symptoms** result from liver injury:
  - But occasional patients have symptoms of acute hepatitis
  - Some patients have changes in mental status that more commonly reflect impaired cerebral perfusion than hepatic encephalopathy

4- **Complications:**
  - Hepatopulmonary syndrome develops in up to 50% of patients but is reversible
  - Occasionally, functional renal failure (increased serum creatinine and potassium, low urinary sodium, and normal urinary sediment) occurs abruptly
  - Fulminant hepatic failure with asterixis and coma:
    - Rare as a complication of heart failure
    - It usually develops 2 - 3 days after the circulatory failure.
    - Serum aminotransferase levels can rise > 1000 U/L.
    - Prognosis is poor; 50% of the patients die of the underlying cardiac disease

Cardiac cirrhosis

1- **Incidence**: rare

2- **The presentation** is usually dominated by symptoms of rightsided heart failure

3- **Cardiac cirrhosis should be suspected** in a patient with:
  - Well-documented tricuspid regurgitation and absent hepatic pulsation

4- **Cardiac cirrhosis should also be considered** in patients with the following:
  - Severe mitral stenosis
  - Constrictive pericarditis
  - Prolonged or recurrent severe congestive heart failure

- Clinically severe passive congestion of the liver, yet a nonenlarged liver, with splenomegaly and ascites

Common causes of combined liver disease and heart disease

1- **Hemochromatosis**:
   - Suggested by an iron saturation > 50%, increased serum ferritin level, an increased hepatic iron index, and the *HFE* gene mutation
2- **Long-term, excessive alcohol consumption:**
   - Can lead to alcoholic cirrhosis and alcoholic cardiomyopathy;
   - The diagnosis is based on the patient's history
3- **The metabolic syndrome:**
   - Characterized by abdominal obesity, hypertension, diabetes mellitus, and dyslipidemia and is associated with nonalcoholic fatty liver disease and atherosclerosis
4- **Hepatitis C:**
   - Diagnosed by antibody to hepatitis C virus (anti-HCV) and by HCV RNA in serum
5- **Amyloidosis**
6- **Hemangioendothelioma**

Laboratory features

Congestive hepatopathy

1- **Bilirubin**
   - Increased serum bilirubin levels occur in **15% - 50% of patients** with heart failure.
   - **Jaundice is usually mild in heart failure**, with serum bilirubin levels generally < 4.5 mg/dL (80 mmol/L)

- Approximately **50% - 60% of the serum bilirubin is unconjugated**, because of a combination of mild hemolysis, reduced uptake, and decreased conjugation by hepatocytes
- **Markedly elevated serum bilirubin levels:**
  - May be seen in acute right-sided heart failure.
  - The hyperbilirubinemia appears to be related to hepatocellular dysfunction per se
- Serum bilirubin levels may fall rapidly after improvement in hepatic congestion, with levels normalizing in **3 - 7 days**
- **In patients with prolonged heart failure:**
  - Serum bilirubin levels may not return to normal for many months after relief of the hepatic congestion because of covalent bonding of conjugated bilirubin with albumin to form *delta bilirubin,* which has a prolonged half-life of 21 days
- An elevated total bilirubin level is an **independent predictor of adverse cardiac** outcome and death in patients with heart failure

2- Aminotransferases

- Levels are elevated in **only 3% - 10% of patients** with stable heart failure without decompensation. Levels are usually two - four times the upper limit of normal
- **Markedly elevated levels** (> 10 times the upper limit of normal) :
  - Seen in patients with acute worsening of severe chronic heart failure, hypotension, or shock, and indicate ischemic hepatitis
- **AST levels tend to be higher than ALT levels**:
  - Because of the AST-rich cardiac myocytes; the increase in AST generally appears earlier than the increase in ALT
- **Very high levels of AST** can also be found in:
  - Patients with drug-induced or viral hepatitis, but ALT levels are usually higher than AST levels in viral hepatitis
- **If the elevation of the AST level is caused by heart failure:**
  - The level can be expected to fall within a few days of circulatory improvement. In contrast, high levels of AST usually persist in cases

of viral or drug-induced hepatitis and are independent of improvement in circulatory status

- **Moderate increases in AST levels:**
  - Can also be caused by myocardial infarction
  - Simultaneous measurement of the troponin or the MB fraction of creatine kinase is helpful in diagnosing myocardial injury
- Improvement in cardiac function results in a return of serum aminotransferase levels toward normal in **3 - 7 days**

3- Alkaline phosphatase

- **Elevated alkaline phosphatase levels are uncommon in heart failure**. When present, the elevation is mild, usually not exceeding twice the upper limit of normal, unless the liver disease and heart failure have a common cause
- **When nodular regenerative hyperplasia** complicates heart failure, the only abnormal liver biochemical test result may be an elevated serum alkaline phosphatase level

4- International normalized ratio (INR)

- This value is **increased in > 80% of patients** with heart failure
- Prolongation of the PT is **more common in acute than chronic** hepatic congestion.
- **In acute congestion**, the PT may increase rapidly to twice normal, is not responsive to vitamin K administration, and may return to normal rapidly with successful treatment of the congestion
- Affected patients are therefore very sensitive to the effects of **warfarin**
- With successful treatment of chronic heart failure, the prothrombin time takes **2 - 3 weeks** to return to normal

5- Serum albumin

- This value is **moderately decreased in 30% - 50% of patients** with heart failure. Lower albumin levels are seen in patients with ascites and edema
- The low serum albumin level **may result** in part from decreased hepatic synthesis and in part from a dilutional effect secondary to fluid retention

- The serum albumin level may require **> 1 month** to improve following resolution of heart failure

Ischemic hepatitis

1- **Changes in serum liver biochemical test** levels in ischemic hepatitis are characteristic

2- **The diagnosis** can be made by observing the following evolution of these changes:

- **Marked increases in aminotransferase** levels with AST > ALT (up to 100 times normal) occur within 24 - 48 hours of the acute circulatory failure
- A rapid **return of the aminotransferase** levels to normal occurs in 3 - 11 days after treatment of acute heart failure
- A profound rise and fall in serum lactate dehydrogenase **(LDH)** levels, moreso than the ALT, and an ALT/LDH ratio < 1.5 are more typical of ischemic hepatitis than of viral hepatitis
- **Alkaline phosphatase** levels generally remain normal
- Serum **bilirubin** levels may rise but are rarely greater than four times the upper limit of normal
- **INR** is only mildly increased

Cardiac cirrhosis

1- No biochemical test distinguishes a congested noncirrhotic liver from one with cardiac cirrhosis

2- Therefore, **cardiac cirrhosis is a clinical and a histologic diagnosis**

Radiologic features

1- **Doppler ultrasonography**

- Biphasic waveforms in the presence of cirrhosis

2- **Contrast-enhanced CT**

- Lobulated, patchy, and inhomogeneous pattern in a large liver
- Irregular perivascular enhancement or delayed parenchymal enhancement

- Distended IVC and early reflux of contrast medium into the IVC and hepatic veins

3- **Transient elastography (Fibroscan)**

- Less reliable in heart failure because liver stiffness measurements are directly related to central venous pressure

Treatment

1- **Treatment of liver congestion:**

- Should be directed toward the primary problem, that is, heart failure
- Improvement in liver biochemical test levels usually follows clinical improvement unless cardiac cirrhosis is already present

2- **Treatment of established cardiac cirrhosis** includes:

- Treatment of heart failure
- Paracentesis if refractory ascites is present
- Regular replacement of albumin after paracentesis is unnecessary because synthetic hepatic function is preserved

3- **Screening for HCC:**

- No recommendations exist for screening for HCC as in other causes of cirrhosis, but cases of HCC arising in cardiac cirrhosis have been reported

4- **Liver biopsy:**

- May be required as focal nodular hyperplasia can be found in patients with cardiac cirrhosis
- The differential diagnosis include:
  - Macronodular regenerative nodules
  - Dysplastic nodules
  - HCC

Cardiac surgery

1- **Clinical improvement in cardiac function** can be dramatic following definitive treatment of heart failure such as:

- Valve replacement

- Pericardiectomy for constrictive pericarditis
- Correction of a congenital anomaly

2- **Cardiac cirrhosis ± hepatic failure:**
- Results in a substantial rise in the perioperative mortality rate and may therefore be a contraindication to surgery

3- **Compensated Child class A patients:**
- Appear to tolerate cardiac surgery satisfactorily

4- **Child class B and C patients:**
- Have high rates of major postoperative complications and death

5- **A Child-Turcotte-Pugh score > 7:**
- Has a high sensitivity (86%) and specificity (92%) for predicting mortality after cardiac surgery with cardiopulmonary bypass and in one study performed better than the MELD score in this setting

6- **Cardiopulmonary bypass:**
- May aggravate preexisting coagulopathy by leading to platelet dysfunction, fibrinolysis, and hypocalcemia.
- Limited evidence suggests that less invasive procedures such as angioplasty, valvuloplasty, and revascularization procedures without bypass are preferable in patients with cirrhosis

7- **Heart transplantation:**
- Liver cirrhosis considered a contraindication to heart transplantation.
- In the few cases of heart transplantation performed in patients with liver cirrhosis, a 50% inhospital mortality rate was reported
- Mortality was highest in patients with a cardiac diagnosis other than cardiomyopathy and in those with a previous sternotomy and massive ascites

Prognosis

1- The prognosis is that of the underlying cardiac disease

2- **In chronic heart failure:**

- The outcome will be favorable if the underlying cardiac condition is treated and the hepatic congestion resolves

3- **In ischemic hepatitis**

- The prognosis is often poor.
- Prolonged jaundice, especially if severe, is a poor prognostic sign
- Death in ischemic hepatitis is usually the result of heart failure. The hepatic disorder usually has little or no influence on the eventual outcome

4- **Cardiac cirrhosis:**

- Does not alter prognosis in general unless cardiac surgery is performed

The liver in systemic disease

Cardiac disease

Heart failure

1- **Effect:**

- The liver may become congested secondary to right-sided heart failure

3- **Manifestations:**

- The patient has a dull ache in the right upper quadrant
- Hepatomegaly is noted in 50% of cases and is associated with splenomegaly or ascites in 10% - 20%.
- Other signs of right-sided heart failure include raised jugular venous pressure and peripheral edema

4- **Laboratory findings:**

- Abnormal liver biochemical test results seen are a raised bilirubin level in 25% - 75% of patients and normal or mildly elevated serum aminotransferase levels.
- The alkaline phosphatase (ALP) is usually (but not always) normal.
- Up to 75% of patients have a prolonged PT

5- Histopathologic examination:

- Enlarged purplish liver
- The cut surface having alternating patches of congested centrilobular regions and pale, less involved areas, the socalled **nutmeg appearance**
- Microscopically, the central veins and centrilobular sinusoids are dilated and engorged with blood; inflammation is not observed.
- Long-standing hepatic congestion can result in extensive fibrosis, so-called **cardiac cirrhosis**.

6- Treatment:

- Treatment of the underlying heart failure normally leads to an improvement in both clinical and laboratory parameters of liver function

Symptoms and signs of hepatic congestion in 175 patients with acute or chronic right-sided heart failure

Manifestations	Acute heart failure (%)	Chronic heart failure (%)
Any hepatomegaly (>11 cm span)	99	95
Marked hepatomegaly (>5 cm below right costal margin)	57	49
Peripheral edema	77	71
Pleural effusion	25	17
Splenomegaly	20	22
Ascites	7	20

Ischemic hepatitis and left-sided HF

1- Definition:

- Hepatic damage associated with acute left ventricular failure is frequently termed ischemic hepatitis.

2- Etiology:

- It usually occurs in the setting of an acute myocardial infarction or cardiogenic shock
- But can result from an abrupt, severe decrease in cardiac output from any cause, as an effect of vasoactive drugs (e.g., cocaine, ergotamine overdosage), or from severe hypoxemia

3- **The major manifestations are biochemical:**

- Elevated serum levels of (AST, ALT) and (LDH) (predominantly hepatic fraction) to 25 or more times the upper limits. Values peak within 1 - 3 days of the inciting event and rapidly return to near normal, usually within 7 - 10 days.
- Serum bilirubin and ALP levels are generally normal or only mildly elevated.
- Liver failure and hepatic encephalopathy can occur

4- **Prognosis:**

- Mortality rates in patients with ischemic hepatitis are high (40% - 50% in some series) but do not correlate with the degree of liver test abnormalities.
- The cause of death is related to the cause of the ischemic injury to the liver, not to liver failure.

5- **Treatment** should be directed to correcting the underlying disease process.

Connective tissue diseases

Polymyalgia rheumatica and giant cell arteritis

1- **Laboratory findings:**

- Elevation of ALP levels occurs in approximately 30% of patients
- Elevated serum aminotransferase levels may also be observed

2- **Liver biopsy:**

- Demonstrate focal hepatocellular necrosis, portal inflammation, and scattered small epithelioid granulomas

3- **Clinically and treatment:**

- The liver abnormalities usually do not cause clinical problems and resolve within a few weeks of the initiation of corticosteroid therapy

Rheumatoid arthritis

1- **Manifestations:**

- Liver disease in rheumatoid arthritis (RA) is most commonly seen in patients with **Felty's syndrome** (splenomegaly and neutropenia in the setting of RA).
- These patients frequently have hepatomegaly

2- **Laboratory findings:**

- Approximately 25% have elevated serum aminotransferase and ALP levels.

3- **Liver biopsy findings:**

- Usually nonspecific: infiltration of portal areas with lymphocytes and plasma cells and mild portal fibrosis
- Some patients with RA develop **nodular regenerative hyperplasia** with atrophy and formation of regenerative nodules that may result in portal hypertension, ascites, and variceal hemorrhage.
- The pathogenesis of nodular regenerative hyperplasia has been proposed to be drug-induced or immune complex-induced obliteration of the portal venules

4- **Treatment:**

- Hepatotoxicity can be associated with salicylates, gold, and methotrexate

Adult Still's disease

1- **Clinical features:**

- This multisystem inflammatory disorder of unknown origin is characterized by spiking fever, evanescent rash, arthritis, and multiorgan involvement including hepatomegaly

2- **Laboratory findings:**

- Abnormal liver enzymes are seen in 50% - 75%; NSAID use may be a significant cofactor

3- **Treatment:**

- After consideration of the possible contribution of medications to hepatic dysfunction, treatment of the underlying disorder with anti-inflammatory drugs, immunosuppressant medications, or biologic agents is indicated

SLE

1- **Clinical features:**
  - Significant liver disease is uncommon
  - Most abnormal liver biochemical test results do not represent clinically significant liver disease

2- **Laboratory findings:**
  - Liver biochemical test abnormalities are common
  - Frequent abnormalities include elevated ALT and ALP levels, normally < 4 times the upper limit of normal.
  - A few patients (approximately 5%) develop jaundice

3- **Causes of liver biochemical abnormalities in SLE are as follows:**
  - **Steatosis** (most common finding on liver biopsy)
  - **Autoimmune hepatitis**, either primary as a result of SLE or coexistent classic autoimmune hepatitis
  - **Autoimmune cholangiopathy**, with an increase in ALP greater than ALT
  - **Nodular regenerative hyperplasia** (may be seen in all connective tissue diseases)
  - **Coexistent viral hepatitis** (in one study, 11% of patients with SLE were positive in serum for hepatitis C viral RNA)
  - **Budd–Chiari syndrome**, particularly in patients with antiphospholipid syndrome
  - **Drugs**, especially methotrexate and salicylates

4- **Treatment:**
  - Drugs suspected of causing abnormal liver biochemical test levels, particularly salicylates, should be withdrawn.
  - Otherwise, the treatment of liver dysfunction in SLE depends on the cause.

Systemic sclerosis (Scleroderma)

1- **From 8% - 15% of patients with systemic sclerosis have antimitochondrial antibodies:**
    - These patients often have evidence of primary biliary cirrhosis on liver biopsy specimens.
    - These changes are more frequent in patients with limited rather than diffuse forms of systemic sclerosis
2- **Nearly 5% of patients with primary biliary cirrhosis:**
    - Have symptoms of systemic sclerosis; which may antedate the diagnosis of primary biliary cirrhosis by many years

Sjogren's syndrome

1- From 5% - 10% of patients with Sj͏ögren's syndrome and approximately 40% with both Sjögren's syndrome and RA have **antimitochondrial antibodies**
    - Most of these patients also have elevated serum ALP levels
2- **Liver biopsy:**
    - Frequently demonstrate changes of stage 1 primary biliary cirrhosis, even in the absence of liver biochemical test abnormalities
3- **Risk of clinical primary biliary cirrhosis:**
    - Uncertain. Whether any early therapeutic intervention is of value is also unclear

Other causes of vasculitis

1- Persons with **polyarteritis nodosa** often have chronic hepatitis **B** virus infection
2- Persons with **cryoglobulinemia** often have chronic hepatitis **C** virus infection

Endocrine and metabolic disorders

Hyperthyroidism

1- **Cholestatic picture :**
    - May occur with untreated cases
2- **Iscemic hepatitis:**
    - May be observed in severe cases as a result of high-output heart failure

3- **Treatment:**

- Propylthiouracil may lead to hepatotoxicity

Type 2 diabetes and the metabolic syndrome

1- **Acute metabolic syndrome:**

- NAFLD may be considered the liver manifestation of the metabolic syndrome of obesity, insulin resistance, hypertension, and dyslipidemia.

2- **Type 2 diabetes:**

- Approximately 60% of patients have evidence of NAFLD, and the frequency increases to > 90% in obese persons

3- **Complications:**

- A subset of patients will develop progressive disease, with an increased risk of the complications of cirrhosis, including hepatocellular carcinoma
- The most common cause of death in such patients remains cardiovascular disease

Granulomatous disease and sarcoidosis

1- **Causes:**

- Systemic infections (e.g., tuberculosis)
- Malignant disease (e.g., Hodgkin's lymphoma)
- Drugs
- Autoimmune disorders (e.g., autoimmune hepatitis)
- Idiopathic conditions (e.g., sarcoidosis)

2- **Laboratory findings of sarcoidosis:**

- Abnormalities of liver biochemical test values are common in sarcoidosis but rarely require treatment. Typically, minor elevations of both aminotransferases and ALP levels are seen

3- **Rarer clinical manifestations include:**

- Chronic intrahepatic cholestasis, portal hypertension, and Budd–Chiari syndrome

4- **Liver biopsy:**

- Demonstrate granulomas in the portal and periportal regions
- Cholestatic and necroinflammatory features may also be seen

5- **Treatment of sarcoidosis:**

- No treatment is required for patients with asymptomatic disease
- Ursodeoxycholic acid, corticosteroids, or methotrexate may be considered in patients with symptomatic disease

Lymphoma and hematologic diseases

Lymphoma

1- **Hodgkin's lymphoma:**

- The liver may be involved in **5%** of patients at presentation but in up to **50%** of patients at autopsy.
- In addition, nonspecific inflammatory infiltrates or noncaseating **granulomas** are seen in the absence of direct hepatic involvement with lymphomas
- An **elevated ALP** level of 1.5 to 2.0 times the upper limit of normal is common even in the absence of direct liver involvement
- **Jaundice is uncommon** in Hodgkin's lymphoma and usually reflects hepatic infiltration with lymphoma, rather than extrahepatic biliary obstruction

2- **Non-Hodgkin's lymphoma :**

- Hepatic involvement is observed in **25% - 50%** of patients; rarely, the liver may be the primary site of involvement.
- Typically, the lymphoma produces a **nodular infiltrate** of the portal areas.
- The clinical and laboratory presentation is similar to that of Hodgkin's lymphoma, except that **extrahepatic obstruction**, usually at the level of the porta hepatis, is much more common

Malignant hematologic conditions

1- **Systemic mastocytosis:**
   - May manifest with hepatosplenomegaly with lymphadenopathy and skin lesions.
   - Liver biopsy specimens show polygonal cells containing eosinophilic granules, predominantly in the portal tracts. Giemsa and toluidine blue staining allows detection of the characteristic **metachromatic cytoplasmic granules**. Periportal fibrosis may also be present.
   - Cirrhosis develops in approximately 5% of patients

2- **Acute lymphoblastic leukemia and acute myeloid leukemia:**
   - Hepatomegaly is common in at diagnosis and is present in 95% and 75%, respectively, of cases post mortem.
   - Liver biopsy is seldom performed because of the high risk of hemorrhage.

3- **Chronic leukemias** (e.g., **chronic lymphocytic leukemia**, **hairy cell leukemia):**
   - Most patients also demonstrate evidence of liver infiltration at autopsy

4- **Multiple myeloma:**
   - Rarely associated with clinically significant liver disease
   - Hepatic manifestations may include diffuse sinusoidal or portal infiltration, nodular regenerative hyperplasia, jaundice, and complications of portal hypertension.
   - Multiple myeloma is also associated with **amyloidosis**

5- **Primary myelofibrosis:**
   - Massive hepatomegaly is seen in **primary myelofibrosis** and other myeloproliferative disorders and is associated with extramedullary hematopoiesis and increased hepatic blood flow.
   - The most common biochemical abnormality is an elevated ALP level, which may be associated with the severity of sinusoidal dilatation

Sickle cell disease

1- **Laboratory findings:**

- Liver biochemical test abnormalities are common
- These abnormalities are frequently caused by other factors such as chronic viral hepatitis or heart failure

2- **Hepatic crisis** usually occurs in the setting of sickle cell crisis

- **Marked by** right upper quadrant pain, jaundice, and tender hepatomegaly
- **Serum bilirubin** levels are frequently as high as 10 - 15 mg/dL and may be as high as 40 - 50 mg/Dl
- **Serum AST and ALT** levels are also elevated, usually up to 10 times normal
- **The LDH** level may be increased markedly, reflecting both liver dysfunction and hemolysis
- **Hemolysis** may contribute to rises in bilirubin and aminotransferase levels, whereas a raised ALP level is often of bone origin
- **Liver biopsy** specimens in hepatic crisis demonstrate sinusoidal distention, erythrocyte sickling, and phagocytosis of erythrocytes by Kupffer cells
- **The differential diagnosis** includes acute cholecystitis and cholangitis
- **Treatment** is supportive and usually results in clinical improvement in a few days, although fatal liver failure has been described

3- **Pigment gallstones :**

- Reported in 40% - 80% of patients with sickle cell disease; choledocholithiasis has been described in 20% - 65% of patients at the time of cholecystectomy
- Abdominal U/S or CT may be helpful in establishing the diagnosis of cholecystitis
- ERCP may be necessary to identify and treat stones in the bile duct

Infections

Overwiew

1- Many systemic infections may cause **abnormalities** in liver biochemical test results, either directly or indirectly.

2- The abnormalities usually **resolve** on resolution of the underlying infection.

3- **Pneumonia:**

  - Often accompanied by elevated liver enzymes.
  - In particular, Legionella pneumophila (causing Legionnaire's disease), Mycoplasma pneumoniae, and Pneumococcus spp. infections may be associated with markedly raised aminotransferase levels and cholestasis

Systemic infection, sepsis and the critically ill patient

1- **Etiology:**

  - Elevated liver enzyme levels are often seen in patients with systemic sepsis.
  - The causes and possible mechanisms are multiple; in most cases, the effect is multifactorial

2- **Intrahepatic cholestasis:**

  - Common in sepsis, independent of the causative organism.
  - Canalicular excretion of conjugated bilirubin is thought to be inhibited by high levels of proinflammatory cytokines, such as tumor necrosis factor-alpha and interleukin-6.
  - Usually, no evidence of cholangitis is seen on liver biopsy specimens

3- **Biochemical findings:**

  - include mildly raised serum ALP levels (one - three times the upper limit of normal) and increased serum bilirubin levels, although these levels may be discordant

4- **Cholestatic drug reaction:**

  - May be associated with antibiotics such as amoxicillin-clavulanic acid and flucloxacillin

5- **Ischemic hepatitis:**

  - May occur in a septic patient as a result of hemodynamic instability

6- **Parenteral nutrition:**

- Associated with hepatotoxicity and NASH, which may be ameliorated by the addition of choline to the formula

HIV infection

1- Approximately 70% of patients with AIDS have clinical **hepatomegaly**, often with abnormal liver biochemical test levels

2- The picture is usually **hepatitic**, with elevation of serum aminotransferases predominating, often related to coinfection with hepatitis B virus or hepatitis C virus

Tuberculosis

1- Miliary tuberculosis:

- May cause hepatitis and rarely jaundice.
- Liver biopsy specimens reveal multiple caseating granulomas

2- Drug therapy:

- Particularly with isoniazid and rifampin, may cause hepatitis with elevated serum aminotransferase levels and jaundice
- Coinfection with HIV or HCV is thought to be an independent risk factor for the development of antituberculous drug–induced hepatitis

Gastrointestinal and nutritional disorders

Celiac disease

1- Findings:

- Serum aminotransferase levels are elevated (< 5 times the upper limit of normal) in 40% of adults with celiac disease at the time of diagnosis.
- Histologic findings in the liver are seen in 66% of these patients but are usually mild and nonspecific

2- Treatment:

- Adherence to a gluten-free diet leads to normalization of serum aminotransferase levels in 75% - 95% of patients, usually within 1 year
- Adherence to a gluten-free diet has generally not been shown to provide benefit in autoimmune associations

3- **Prognosis:**

- Celiac disease may be associated with an increased risk of death from liver cirrhosis

Liver diseases associated with celiac disease

1- Isolated elevation of the aminotransferase levels (celiac hepatitis), reversible on gluten-free diet
2- Cryptogenic cirrhosis
3- Autoimmune liver disorders
    - Primary biliary cirrhosis
    - Autoimmune hepatitis: type 1 and type 2
    - Autoimmune cholangitis
    - Primary sclerosing cholangitis
4- Chronic hepatitis C
5- Hemochromatosis
6- Nonalcoholic fatty liver disease
7- Acute liver failure
8- Regenerative nodular hyperplasia
9- Hepatocellular carcinoma

Liver abnormalities in IBD

1- **Laboratory findings:**

- Abnormal hepatic biochemistry values (mild elevations of serum aminotransferase and ALP levels) are common in patients with IBD, with a frequency of approximately 30%.
- In a large series, abnormal hepatic biochemistry was associated with increased mortality, but not with disease activity, although the reason for the increased mortality was unclear

2- **Liver biopsy:**

- **Steatosis** is the most commonly observed
- Additionally, **chronic hepatitis** characterized by either portal or lobular infiltrates of mononuclear inflammatory cells may be found.

It is not clear whether hepatitis is a direct consequence of IBD or a manifestation of PSC or another cause of liver disease such as hepatitis C or drugs.

- The frequency of **autoimmune hepatitis** is increased in patients with inflammatory bowel disease
- Patients with Crohn's disease infrequently develop hepatic **granulomas** or **amyloidosis.**

Biliary abnormalities in IBD

1- **PSC :**

- The most important hepatobiliary complication of inflammatory bowel disease
- It occurs in 5% - 10% of patients with ulcerative colitis but in fewer than 1% of those with Crohn's disease

2- **The only sign of early PSC:**

- May be an elevated serum ALP level.
- Patients with more advanced disease may present with pruritus or jaundice

3- **Complications of PSC:**

- Progression varies widely among affected persons, possibly related to an individual's HLA status.
- Most patients ultimately develop **biliary cirrhosis** with increasing serum levels of bilirubin and ALP and portal hypertension with ascites and variceal bleeding.
- **Bacterial cholangitis** may also be observed, particularly in patients who have undergone surgical or endoscopic intervention of the bile ducts
- Up to 20% of patients with PSC develop **cholangiocarcinoma**

4- **Diagnosis of PSC:**

- Visualization of the biliary tree by ERCP or MRCP.
- The typical pattern is of multiple bile duct strictures with areas of beaded dilatation.

- Distinguishing benign strictures from cholangiocarcinoma by radiographic criteria is often difficult. Brush cytology and biopsy obtained at ERCP may be helpful

5- **Treatment:**
    - Neither medical nor surgical treatment of the underlying IBD alters the course of PSC.
    - Treatment with ursodeoxycholic acid may result in some improvement in symptoms and liver biochemical test values.
    - Patients with advanced liver disease secondary to PSC may be candidates for **liver transplantation** if they have not already developed cholangiocarcinoma, although PSC may recur in the graft

Obesity

1- Closely associated with insulin resistance and NAFLD

2- The mainstay of treatment is:
    - Weight loss by dietary restriction.
    - Bariatric surgery (gastric bypass or banding) reduces the severity of NASH in obese patients

Anorexia nervosa

1- **Laboratory findings:**
    - Up to 30% of patients with moderately severe (body mass index 12 - 16) and 75% of those with severe (body mass index < 12) anorexia nervosa have raised aminotransferase levels
    - Marked increases are often a marker of impending multiorgan failure

2- **Treatment:**
    - Transient increases in liver enzyme levels may occur during refeeding in patients with anorexia nervosa and other causes of starvation
    - The abnormalities resolve completely when refeeding is completed

Amyloidosis

Definition

1- Systemic amyloidosis is characterized by the **extracellular deposition** of fibrillar protein in many tissues.

2- It may be classified as **AL (primary amyloid**) and **AA (secondary amyloid)**, accounting for approximately 90% of cases.

3- The amyloid protein is seen as green birefringent extracellular material when stained with **Congo red dye** and viewed under polarized light

Types

1- **Primary amyloidosis**

- Represent approximately 80% of all cases
- The amyloid consists of kappa or lambda immunoglobulin light chains produced by a monoclonal population of plasma cells.
- Bence Jones proteinuria may also be present, and approximately 1/3 of patients have multiple myeloma

2- **Secondary amyloidosis**

- The amyloid is derived from serum amyloid A, secreted by the liver as an acute phase reactant in response to chronic infections or inflammatory processes such as tuberculosis, lepromatous leprosy, osteomyelitis, RA, Crohn's disease, or lymphoma

Clinical Presentation

1- **Usually nonspecific**, and patients may present with symptoms related to deposition of amyloid in other organs:

- Heart failure
- Nephrotic syndrome
- Intestinal malabsorption
- Peripheral or autonomic neuropathy
- Carpal tunnel syndrome

2- **Hepatic amyloidosis:**

- Should be suspected in patients with hepatomegaly in the setting of a chronic infectious or inflammatory process, particularly if it is associated with proteinuria or monoclonal gammopathy

3- **Hepatomegaly** (passive congestion or infiltration) is found in up to 60% of affected patients

4- **Splenomegaly** is much less common (approximately 5%).

Abnormalities of biochemical tests

1- Marked increase in serum ALP levels, with aminotransferases less than twice normal.

2- The serum albumin level may be low, often secondary to proteinuria, which may be in the nephrotic range in 30% of patients

Liver biopsy

Should be **avoided**, if possible, because of an increased risk of bleeding after biopsy

Prognosis and treatment

1- Prognosis of patients with systemic amyloidosis is generally **poor**, with a median survival of < 2 years.

2- **Mortality** is usually the result of cardiac or renal disease and only rarely hepatic involvement.

3- **Treatment** of predisposing chronic inflammatory conditions may improve the outcome

The liver in systemic disease

Disorder(s)	Hepatic manifestations	Liver biochemical test levels (most common abnormalities)
Cardiovascular		
Heart failure	Vascular congestion; hepatomegaly	↑Bil; ↑ALT; ↑PT
Ischemic hepatitis	Hepatocellular necrosis	↑↑↑ALT; ↑Bil
Connective Tissue		
Polymyalgia rheumatica and giant cell arteritis	Hepatocellular necrosis; portal inflammation	↑ALP; ↑ALT
Rheumatoid arthritis; Felty's syndrome; adult Still's disease	Nonspecific: portal inflammatory infiltrates and fibrosis; drug hepatotoxicity	↑ALP; ↑ALT
Systemic lupus erythematosus	Autoimmune hepatitis; autoimmune cholangiopathy; nodular regenerative hyperplasia; drug hepatotoxicity	↑↑ALP; ↑Bil; ↑↑ALT
Systemic sclerosis; Sjogren's Syndrome	Budd–Chiari syndrome; antimitochondrial antibodies; primary biliary cirrhosis	↑↑ALP; ↑Bil; (↑)ALT
Endocrine and Metabolic		

Hyperthyroidism	Nonspecific inflammation and cholestasis	↑ALP; ↑ALT; ↑GGTP
Type 2 diabetes mellitus	Steatosis; steatohepatitis	↑ALT; ↑GGTP
Gastrointestinal and Nutritional		
Celiac disease (see Table.)	Elevated aminotransferase levels; association with primary biliary cirrhosis, autoimmune hepatitis, and PSC; jaundice	↑ALT
Inflammatory bowel disease	Association with PSC, cholangiocarcinoma; hepatic steatosis; immunosuppressant medication hepatotoxicity; jaundice	↑ALT
Anorexia	Steatosis; liver failure	↑ALT
Obesity	Steatosis; steatohepatitis	↑ALT; ↑GGTP
Granulomatous		
Sarcoidosis	Epithelioid granulomas	↑↑ALP; ↑ALT
Hematologic		
Lymphomas, acute and chronic leukemias, myeloproliferative disorders (including myelofibrosis)	Hepatomegaly; infiltration; extrahepatic biliary obstruction	↑ALP; ↑Bil
Sickle cell disease	Hemolysis; ischemia; pigment cholelithiasis	↑↑Bil; ↑ALP; ↑ALT
Infections		
Sepsis	Intrahepatic cholestasis; ischemic hepatitis; drug hepatotoxicity	↑Bil; ↑ALP; ↑ALT
HIV infection	Hepatomegaly; coinfection with hepatitis B or C	↑ALT
Tuberculosis	Caseating granulomas; drug hepatotoxicity	↑ALT; ↑↑Bil; ↑ALP
Pneumonia	Nonspecific inflammatory changes	↑↑Bil; ↑ALP
Amyloidosis	Infiltration; vascular congestion	↑↑ALP; ↑ALT

Rheumatological manifestations of liver and GIT diseases

Disease	**Effect**
HBV	Arthralgias Polyarteritis nodosa
HCV	Arthralgias Arthritis (mono- or polyarthritis) Polyarteritis nodosa SLE Fibromyalgia
Wilson's disease	Osteopenia Arthropathy Chondrocalcinosis
Hemochromatosis	Chondrocalcinosis (esp. 2nd , 3rd MCP joints) Osteopenia Subchondral cyst formation

Liver cirrhosis	Hepatic osteodystrophy Hypertrophic osteoarthropathy
PBC	Osteoporosis Arthropathy
PSC	Rheumatoid arthritis/arthropathy
Autoimmune hepatitis	Synovitis Rheumatoid arthritis SLE
Inflammatory bowel disease	Peripheral arthritis Sacroiliitis Ankylosing spondylitis
Malabsorption syndrome	Osteoporosis Osteomalacia
Whipple's disease	Seronegative large joint arthritis (Precedes intestinal symptoms in most patients) Sacroiliitis
Celiac disease	Systemic lupus erythematosis Rheumatoid arthritis

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